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High Flow Nasal Therapy vs Conventional Oxygen Therapy in Mild COVID-19 Hypoxaemia: A Bayesian Reanalysis of the COVID-HIGH Trial

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ABSTRACT

Background

Clinical effectiveness of high-flow nasal therapy (HFNT) over conventional oxygen therapy (COT) in patients with mild COVID-19-related acute hypoxaemic respiratory failure (AHRF) remains uncertain. The COVID-HIGH trial did not demonstrate statistically significant benefits of HFNT over COT. However, the trial was slightly underpowered, and the event rate lower-than-expected. Bayesian methods provide deeper insight by incorporating prior knowledge and quantifying uncertainty intuitively. This analysis aimed to quantify the probability of benefit or harm associated with HFNT, adopting a Bayesian approach.

Methods

We performed a Bayesian reanalysis of the COVID-HIGH trial (NCT, which randomised 364 patients with $\text{PaO}_2/\text{FiO}_2$ between 200–300 mmHg to receive HFNT or COT. The primary outcome was escalation of respiratory support (continuous positive airway pressure, noninvasive ventilation or invasive mechanical ventilation) within 28 days. A key secondary outcome was clinical recovery at day 14. Bayesian logistic models with noninformative and informative priors were used to estimate the posterior probability of treatment effects.

Results

Escalation of respiratory support occurred in 23.6% (HFNT) versus 30.2% (COT) (risk difference -6.6% , 95% CI -15.1 to 2.1 ; $p=0.14$).

Across a wide range of priors, the posterior probability mass on the beneficial side remained high, generally $>70\%$, while the proportion on the harm side remained consistently low at $\leq 6\%$ for all models, underscoring a favourable benefit-risk profile.

The acute respiratory failure meta-analysis model (OR 0.76, 95% CrI 0.60 - 0.97), the COVID-19 randomised evidence model (OR 0.76, 95% CrI 0.60 - 0.97), the COVID-19 observational evidence model (OR 0.60, 95% CrI 0.45 - 0.80), and the COVID-19 Bayesian meta-analysis mixed evidence model (OR 0.66, 95% CrI 0.52 - 0.86) showed posterior probability mass on the beneficial side of 70% - 94%. Clinical recovery at day 14 occurred in 61.5% (HFNT) versus 53.3% (COT), with 61-73% of posterior probability mass on the clinical benefit side.

Conclusions

This Bayesian re-analysis of the COVID-HIGH trial suggests that HFNT likely reduces escalation of respiratory support and improves clinical recovery in patients with COVID-19 pneumonia and mild hypoxaemia, although the magnitude of benefit remains uncertain and sensitive to prior assumptions.

Trial registration: The trial was prospectively registered in ClinicalTrial.gov on December 7, 2020 (NCT04655638)

Keywords: high-flow nasal therapy, acute hypoxemic respiratory failure, mild hypoxemia, COVID-19 pneumonia, Bayesian statistics.

INTRODUCTION

Acute hypoxaemic respiratory failure (AHRF) is a frequent and life-threatening manifestation of COVID-19, often requiring escalation from conventional oxygen therapy (COT) to advanced respiratory support, including high-flow nasal therapy (HFNT), continuous positive airway pressure (CPAP), noninvasive ventilation (NIV) or invasive mechanical ventilation (IMV). While HFNT has demonstrated efficacy in reducing intubation rates and improving clinical outcomes in patients with moderate-to-severe AHRF of non-COVID aetiology, evidence supporting its benefit in patients with mild hypoxaemia due to COVID-19 remains limited and uncertain (1–7).

The COVID-HIGH trial was the first large multicentre randomised controlled trial (RCT) specifically designed to evaluate whether HFNT, compared with COT, reduces the risk of escalation of respiratory support in patients with COVID-19 and mild hypoxaemia (7,8). Although COVID-HIGH did not demonstrate a statistically significant difference in its primary outcome, frequentist analysis may not fully capture the uncertainty surrounding treatment effects, especially in trials with modest event rates or potential for type II error. Indeed, the trial was underpowered for the primary outcome due to a pre-planned sample size calculation based on available data at the beginning of the pandemic (9).

Bayesian methods offer an alternative framework that incorporates prior knowledge and directly quantifies the probability of clinically important benefits or harms, thus providing a more nuanced interpretation of trial results (10). Recent studies have demonstrated how Bayesian re-analyses can recontextualise findings from large RCTs by integrating external evidence or exploring the impact of different prior assumptions on the estimated treatment effects.

Therefore, we performed a Bayesian re-analysis of the COVID-HIGH trial to estimate the probability that HFNT reduces the risk of escalation of respiratory support or influences other clinically relevant outcomes. This re-analysis aims to complement the original frequentist results by offering a probabilistic interpretation of HFNT's potential benefits or harms in patients with COVID-19 and mild hypoxemia, which may guide clinicians in selecting appropriate respiratory support strategies in this population.

METHODS

We reanalysed data from the COVID-HIGH trial, which enrolled 364 adult patients (≥ 18 years) with confirmed COVID-19 pneumonia and mild hypoxaemic respiratory failure, defined as $\text{PaO}_2/\text{FiO}_2$ between 200–300 mmHg. Patients were randomised to receive either HFNT or COT. Full details on trial design and patient characteristics are available in the original COVID-HIGH trial primary results manuscript (Trial registration number NCT04655638) (8).

We conducted Bayesian analyses following the framework outlined by Zampieri et al., employing generalised linear models to evaluate the effect of the intervention—HFNT versus COT—on both the primary and one selected secondary outcome (10).

The primary outcome was defined as the proportion of patients requiring escalation of respiratory treatment, i.e., CPAP, NIV, or IMV, within 28 days. The secondary outcome chosen for Bayesian analysis was the proportion of patients who terminated the study protocols due to improvement (clinical recovery, defined as the improvement in oxygenation with the ability to maintain $\text{SpO}_2 \geq 96\%$ with $\text{FiO}_2 \leq 30\%$

or $\text{PaO}_2/\text{FiO}_2$ ratio >300 mmHg). Patients and public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

The trial was prospectively registered in ClinicalTrial.gov on December 7, 2020 (NCT04655638). The study protocol of the original COVID-HIGH trial was approved by the Ethics Committee of the coordinating centre (Comitato Etico Catania 1, 01/2021/PO, 25/01/2021) and all participating sites before patient inclusion. The study was performed in accordance with Good Clinical Practice guidelines and ethical principles of the Declaration of Helsinki. The trial was overseen by an oversight committee comprised of independent clinicians with no competing interests. Written informed consent was obtained from all patients or surrogates.

Model Structure and Prior Specification

We implemented the regression models using the brms package (version 2.22.0) in the R statistical computing environment (R version 4.5.1, R Core team, 2023), interfacing with the Stan probabilistic programming language (11–15). For each outcome, we fitted a Bayesian model using the Beta-Bernoulli conjugate framework to estimate the outcome probabilities in each group, using priors that reflected different levels of prior belief strength, including sceptical, optimistic, and flat specifications. We did not include clinical or enrolment site covariates in our linear models (see Supplementary Material for an example of brms model). Prior distributions were defined as Normal distributions on the natural log-odds ratio ($\log(\text{OR})$) scale. The mean of the distribution represented the expected treatment effect, while the standard deviation (SD) encoded the strength of belief in that effect: smaller SDs indicated stronger prior certainty. Specifically, we defined four levels of

prior informativeness: strong prior (SD = 0.1), moderately strong or intermediate prior (SD = 0.4), weak prior (SD = 0.8), and flat non-informative prior (SD = 1000).

The clinical translation of the priors based on Cohen's effect sizes for the primary outcome, escalation of respiratory support, assumes a control event rate of 38.6%. Under this baseline risk, a small effect size corresponds to an absolute change of approximately 9 to 10 events per 100 patients, either as a reduction or an increase in escalation rates. A moderate effect size corresponds to an absolute change of roughly 22 to 25 events per 100 patients. A large effect size corresponds to a substantial absolute change of approximately 31 to 38 events per 100 patients.

Strong priors based on arbitrary effect size values were designed solely to assess the robustness of our data across a wide range of prior values and were not considered clinically plausible.

For flat/non-informative analysis, we used priors centred at $\log(\text{OR}) = 0$ with SD = 1000. For informative priors, the prior mean was derived from expected effect sizes defined using Cohen's h , a standardised measure of difference in proportions. We categorised effect sizes as follows: small ($h = 0.2$), moderate ($h = 0.4$), and large ($h = 0.8$). Expected treatment effects were converted to $\log(\text{OR})$ values using the arcsine square root transformation, assuming known event rates in the control (COT) group, 38.6% for the primary outcome and 60.7% for the secondary outcome.

All models were run using four Markov Chain Monte Carlo (MCMC) chains with 20,000 iterations each. Convergence was assessed using the Gelman–Rubin statistic (R -hat) and by visual inspection of trace plots and overlay density plots, generated using the bayesplot package (16,17).

Meta-analysis-derived informed priors

To derive an informative prior distribution, we performed a frequentist meta-analysis based on escalation data reported by Seow et al., who found that HFNT reduced escalation to IMV (risk ratio (RR) 0.85; 95% confidence interval (CI) 0.76-0.95; $p=0.004$) and NIV (RR 0.69, 95% CI 0.49, 0.99; $p=0.04$) compared to COT in patients with acute respiratory failure (18).

Data on escalation to both non-invasive and invasive mechanical ventilation were extracted from published forest plots and combined.

Using the meta R package, we performed a quantitative synthesis using a random-effects model with the inverse-variance method and the restricted maximum-likelihood estimator for τ^2 , based on data from 36 studies, 8428 patients, and 3091 escalation events(5,19–53). The random-effects model estimated the effect size as OR 0.8 (95% CI 0.59 -1.07, p -value 0.13). The quantitative synthesis showed signs of heterogeneity, with $I^2 = 73.2\%$ (CI 62.8 - 80.7%; Supplementary Figure 1). Based on these results, we developed a model based on an informed normal prior centred at $\log(\text{OR}) = -0.22$ with $\text{SD}=0.15$.

We extracted data from a systematic review by Wang et al. that focused on patients with acute respiratory failure due to COVID-19 undergoing HFNO or conventional oxygen therapy, with escalation to IMV as the primary outcome (54).

We performed a frequentist meta-analysis of observational studies of COVID-19 patients and a separate meta-analysis of RCT data (5,22,28–30,40,47,49,55–62).

The quantitative synthesis of observational studies included 9 studies, 3005 patients, 1782 events (Supplementary Figure 2).

The random-effects model estimated the effect size as OR 0.52 (95% CI 0.35 - 0.78, p-value 0.0013) with significant heterogeneity, $I^2 = 81.1\%$ (CI 65.1 - 89.8%).

Based on these results, we developed a model based on an informed normal prior centred at $\log(\text{OR}) = -0.63$ with $\text{SD}=0.20$.

The quantitative synthesis of randomised studies included 6 studies, 2180 patients, 835 events (Supplementary Figure 3).

The random-effects model estimated the effect size as OR 0.8 (95% CI 0.59 - 1.07, p-value 0.1359) with significant heterogeneity, $I^2 = 47.9\%$ (CI 0 - 79.3%).

Based on these results, we developed a model based on an informed normal prior centred at $\log(\text{OR}) = -0.23$ with $\text{SD}=0.15$.

We also performed a Bayesian meta-analysis of COVID-19 RCTs using the bayesmeta package (63). The meta-analysis was based on an informed a priori using the results of the aforementioned pooling of nonrandomised data. The Bayesian meta-analysis estimated the mean posterior effect size as OR 0.65 (95% CrI 0.47 - 0.88), with significant heterogeneity ($I^2 = 59\%$, Supplementary Figure 4).

Based on these results, we developed a model based on an informed normal prior centred at $\log(\text{OR}) = -0.43$ with $\text{SD}=0.16$.

To the best of the authors' knowledge, there is insufficient evidence to perform a quantitative synthesis limited to patients with mild COVID-19 respiratory failure, so we considered the aforementioned meta-analyses the best available sources of data for designing our informed priors.

Posterior Inference and Visualisation

Posterior distributions were summarised using the posterior means and 95% Highest Density Intervals (HDIs) (64). We visualised the prior, posterior, and approximate likelihood distributions on the log-odds scale. The marginal likelihood was approximated using a profile likelihood method (65). All plots were generated with `ggplot2` package in R (66). Posterior estimates are reported as OR with corresponding 95% credible intervals (CrI), which represent the range within which the true parameter value lies with 95% probability, given the data and the model.

Region of Practical Equivalence (ROPE)

To guide interpretation of the posterior distributions, we applied the Region of Practical Equivalence (ROPE) framework, following the approach described by Kruschke et al. (64,67–69). The ROPE was defined as the range of effect sizes considered clinically negligible, corresponding approximately to a Cohen's h value between +0.1 and -0.1. For each posterior distribution, we quantified the proportion of the probability mass falling into the following three regions:

- Within the ROPE (no clinically relevant effect),
- Beyond the ROPE in the beneficial direction (potential benefit),
- Beyond the ROPE in the harmful direction, including a predefined threshold for severe harm, set at $\log(1.25)$ (corresponding to a 25% increase in odds).

To better quantify the effect size of the ROPE region for the primary outcome, escalation of respiratory support, the effect size corresponds to a reduction or excess of about 5 per 100 treated patients compared with the control. Given limited resources during the COVID-19 pandemic, we believe this effect size is clinically negligible.

Model Comparison and Bayes Factor

We compared each pair of models, calculating the Bayes Factor (BF), through the brms package.

The BF represents the ratio of the marginal likelihoods of two models —that is, the probability of the observed data under each model, accounting for their prior distributions. It quantifies the evidence in favour of one hypothesis over another by showing how much more likely the observed data are under one model compared to the other. To categorise the strength of evidence in favour of one model over another, we used Jeffrey's framework for BF interpretation, as reported by Kelter (70,71).

Quantitative synthesis

We used forest plots to show the posterior estimates and assess consistency across models. The analysis was performed using bayesmeta and ggplot2 packages in R, and we assessed the between-model heterogeneity using the metric tau, which reflects dispersion across model estimates and is influenced by prior specifications (63,66).

All Bayesian analyses were implemented in R (version 4.5), using the brms package (version 2.22.0), Stan as the backend sampler, and visualisations produced using ggplot2 (11–14,66). Custom R code was developed to convert Cohen's h values to log ORs and to generate prior and posterior plots incorporating ROPE assessments. The code used for ROPE visualisations was partially adapted from Zampieri's methodological paper (10).

RESULTS

The analyses conducted revealed varying probabilities of clinical benefit based on different prior models, with substantial evidence supporting modest overall benefits despite significant sensitivity to the chosen prior.

Escalation of respiratory support

Details on the models, priors, and results are reported in **Additional file 1** (Supplementary Figures 4-10 and Supplementary Table 1). The Gelman–Rubin diagnostic (R-hat) values approached unity for all models, indicating satisfactory convergence of the MCMC simulations (see **Additional file 1** - Supplementary Figures 12-13). Both bulk Effective Sample Size and tail Effective Sample Size values were sufficiently large relative to the total number of post-warm-up draws, indicating low autocorrelation and reliable estimation of central tendencies and distribution tails.

The flat prior model yielded a posterior estimate corresponding to an OR of approximately 0.69 (Supplementary Figure 5). The mass probability in the benefit area was 77.5%, and in the ROPE area, 22.1%. Under weak scepticism (SD = 0.8), the probability mass in the clinical benefit range remained relatively high at 74%, with a ROPE probability of 25%. However, as prior scepticism intensified, with intermediate (SD = 0.4) and strong (SD = 0.1) priors, the probability mass on the benefit side declined to 65.8% and 6.3%, respectively, while ROPE probabilities surged to 33.6% and 93.6%, respectively (Supplementary Figure 5-6).

Under the large-effect optimistic priors, we observed a high proportion of posterior probability allocated to the benefit range (91.6-100%). Optimistic moderate effect

and small effect models yielded a high proportion of posterior probability on the clinical benefit side, ranging from 78.9% to 100%.

The Strong Optimistic Small Effect Size Model (mean 0.42, SD 0.1) resulted in a posterior estimate of OR 0.66 (CrI 0.55, 0.79, Supplementary Figures 7-8).

Under pessimistic models with weak priors, data partially counteracted prior assumptions, with the probability mass in the clinical benefit range ranging from 70% to 53.8%. However, strong pessimistic priors (SD = 0.1) completely overwhelmed the data, yielding a 100% probability of harm (Supplementary Figures 9-10).

Using the normal prior derived from a combined respiratory failure meta-analysis, including randomised and non-randomised evidence, centred at $N(-0.22, 0.15)$, the posterior mean log odds ratio was -0.27 , corresponding to an odds ratio of approximately 0.76 (Figure 1). The proportion of posterior probability on the benefit side was 70.1%, while 29.9% of the posterior mass laid within the ROPE (Figure 2). No posterior probability supported harm. This indicates a predominance of clinically relevant benefit, though a non-trivial proportion is compatible with no meaningful effect.

The meta-analysis model, derived primarily from non-randomised COVID-19 studies and with a stronger prior centred at $N(-0.63, 0.2)$, yielded a posterior mean of -0.52 , corresponding to an odds ratio of approximately 0.60. This model showed very high posterior support for a beneficial effect, with 98.3% of the posterior probability on the beneficial effect side and only 1.7% within the ROPE. No probability mass was located on the harm side.

The meta-analysis models that relied solely on randomised evidence produced more cautious yet consistent results. The frequentist COVID-19 RCT-derived prior $N(-0.23, 0.15)$ returned a posterior mean logOR of -0.27 , corresponding to an odds ratio of approximately 0.76 . The posterior probability of benefit was 70.5% , with 29.5% within the ROPE and no support for harm. Similarly, the Bayesian COVID-19 meta-analysis derived prior $N(-0.43, 0.16)$ resulted in a posterior mean of -0.41 , corresponding to an odds ratio of approximately 0.66 , with 94.3% of the posterior probability supporting benefit and 5.7% within the ROPE.

Across all meta-analysis-informed models, posterior probability mass overwhelmingly favoured benefit, with no evidence of harm. Models based on randomised or mixed evidence consistently supported a small to moderate benefit, with residual uncertainty about clinical irrelevance. Still, these three models showed overlap between the HDI and the ROPE, indicating that the null hypothesis cannot be definitively rejected. In contrast, the model informed by non-randomised evidence yielded stronger posterior support for benefit and less probability within the ROPE, also with no overlap between the HDI and the ROPE. Using the strong sceptical null prior (SkOS $N(0, 0.1)$) as the reference model to represent the null hypothesis, the Bayes factor results indicate consistent, though generally modest, support for at least a small benefit. The strongest evidence against the null is observed for the Strong Optimistic Small Effect Size model $N(-0.42, 0.1)$, which yields a Bayes factor of 3.07 relative to SkOS, corresponding to moderate evidence in favour of a small beneficial effect. The Intermediate Optimistic Small Effect Size model $N(-0.42, 0.4)$ also favours benefit, with $BF = 1.67$ relative to the null, whereas the weak small effect model $N(-0.42, 0.8)$ does not improve fit relative to no difference, with $BF = 0.92$.

Meta-analysis-informed models showed a coherent and broadly similar pattern. The Bayesian meta-analysis model $N(-0.43, 0.16)$ received moderate support vs the null model with a $BF = 2.74$ (Supplementary Figure 11). Meta-analysis models derived from COVID-19 randomised studies and the mixed evidence on acute respiratory failures, centred on $N(-0.22, 0.15)$, perform similarly, with Bayes factors of 2.47 relative to $Sk0S$. The meta-analysis model, based primarily on non-randomised studies, centred on a larger effect $N(-0.63, 0.2)$, received weaker support, with $BF = 1.73$ versus the null. Overall, when evaluated against a tight null prior, our data consistently favoured models with priors centred on modest effect sizes with relatively limited dispersion (Supplementary Figure S15 in the **Additional file 1**).

Models assuming large or moderate effect sizes, or using flat priors, yielded less consistent support for benefit, as reflected by lower Bayes Factors.

Across models, we found that the pooled posterior effect estimate was centred at $\log(OR) = -0.25$, corresponding to an OR of approximately OR 0.78 (CrI 0.62 - 0.98), suggesting a modest overall benefit (**Figure 3**). However, the level of heterogeneity was notable, with median $\tau = 0.61$ and an associated I^2 of 95%, indicating that the Bayesian estimates were quite sensitive to prior specification.

Clinical Recovery

Details on the models, priors, and results are reported in Supplementary Figures 14-19 and Supplementary Table 2 in the **Additional file 1**. The Gelman–Rubin diagnostic (R-hat) values were all equal to 1, suggesting satisfactory convergence of the MCMC chains (Supplementary Figures 21-22 in the **Additional file 1**). The sceptical models with flat-to-moderate strength priors showed a posterior probability mass on the clinical benefit side ranging from 72.6% to 60.8%. The optimistic models

yielded a proportion of the posterior probability lying beyond the ROPE on the beneficial side, ranging from 74.4% to 98.6%. The Strong Optimistic Small Effect Size N (0.42, 0.1) produced a posterior estimate of OR 1.5 (CrI 1.27, 1.83; Figure 3), with 98.6% of the posterior probability allocated to the clinical benefit range. Pessimistic models showed that evidence of clinical benefit remained robust under weak and intermediate strength targeting small effects, with 65% to 41.9% of the posterior probability within the benefit range, and less than 3% indicating harm. The Strong Optimistic Small Effect Size N (0.42, 0.1) and Intermediate Optimistic Small Effect Size: N (0.42, 0.4) showed robust evidence ($BF > 10$) against most alternatives (Supplementary Figure 20 in the **Additional file 1**). The weakest supporting evidence was observed for both optimistic and pessimistic models assuming large effect sizes, as well as flat prior model.

Quantitative synthesis across models yielded a pooled posterior mean effect of OR 1.23 (CrI 0.94 -1.60) with significant prior-related heterogeneity (**Figure 4**).

DISCUSSION

In this post hoc analysis of the COVID-HIGH trial, we used a Bayesian approach to re-interpret the original results. Our analysis suggests a high probability that HFNT is clinically beneficial compared to COT in reducing the need for escalation of respiratory support.

Across a wide range of prior assumptions – from flat to optimistic – the posterior probability mass on the clinical benefit side remained high (generally $>70\%$), while the posterior probability mass on the clinically meaningful harm side remained consistently low ($\leq 6\%$) across all models, underscoring a favourable benefit-risk profile. Even under weakly sceptical priors, the data suggested a substantial

likelihood of clinical benefit. Although strong sceptical priors could attenuate the observed effect, these scenarios represent assumptions that are not aligned with the available empirical evidence. Moreover, under weak to intermediate sceptical models, HFNT promotes timely clinical recovery, with a probability mass in the benefit region ranging from 61% to 73%. These findings mitigate the conclusion of the original frequentist analysis, which may overlook potentially meaningful effects (8). Therefore, we sought to better characterise the likelihood of clinical benefit or harm associated with the use of HFNT in patients with COVID-19 pneumonia and mild hypoxaemia in a probabilistic framework.

Unlike p-values, which provide binary outcomes, our Bayesian approach quantifies the probability mass lying on the side of benefit or harm, offering clinicians a more intuitive basis for decision-making (72).

These Bayesian findings should be interpreted as complementary to the primary frequentist analysis of the COCID-HIGH trial.

Across multiple meta-analysis-informed prior specifications, results were consistent and favoured a reduction in escalation of respiratory support. Using a respiratory failure meta-analysis combining randomised and non-randomised studies, the posterior log odds ratio was -0.27 , corresponding to an odds ratio of approximately 0.76, with 70.1% of the posterior probability supporting benefit and 29.9% within the ROPE.

Similar results were observed when restricting the prior to randomised COVID-19 evidence. The COVID-19 RCT frequentist meta-analysis prior yielded a posterior odds ratio of approximately 0.76, with 70.5% of probability mass in the benefit area and 29.5% within the ROPE. The Bayesian COVID-19 RCT meta-

analysis, incorporating information from non-randomised studies, produced a stronger effect on the posterior effect size, with an odds ratio of approximately 0.66 and 94.3% posterior probability supporting benefit, with only 5.7% within the ROPE.

The meta-analysis-derived prior, based predominantly on non-randomised COVID-19 studies, showed the largest effect, with a posterior odds ratio of approximately 0.60 and a 98.3% posterior probability supporting benefit. Across all meta-analysis designs, no posterior probability supported harm, indicating robust support for benefit with varying degrees of certainty depending on the source of prior information. Among all the meta-analysis models, only the COVID-19 non-randomised informed prior showed HDI values outside the ROPE region.

These findings support existing international guidelines suggesting the efficacy of HFNT in reducing intubation or escalation of care in acute respiratory failure and are particularly relevant when considered in the context of the COVID-19 pandemic, during which ICU resources were often critically limited (2,3,73).

The findings of the present study align with a growing body of literature supporting the use of Bayesian approaches in critical care trials, particularly in situations where modest or lower-than-expected event rates compromise statistical power. The increasing adoption of Bayesian methods in critical care trials reflects a shift toward more informative, decision-oriented interpretations of clinical evidence (74). Several high-profile RCTs in intensive care, such as ANDROMEDA-SHOCK, EOLIA, and RECOVERY, have been reanalysed using a Bayesian approach to address the limitations of conventional frequentist null hypothesis testing, especially in the context of modest effect sizes (75–77). These re-analyses have shown that trials deemed "negative" by conventional standards may still suggest high probabilities of clinically meaningful benefit when viewed through a Bayesian

framework. Our findings contribute to this evolving methodological landscape, reinforcing the value of probabilistic inference in trials with lower-than-expected event rates or underpowered designs, which are common challenges in acute care research.

The application of the ROPE allowed us to further assess the degree to which treatment effects were clinically meaningful. In most models, only a minority of posterior probability fell within the ROPE, suggesting that the observed effects of HFNT are unlikely to be clinically negligible. Still, many models showed an HDI interval that partially overlapped the ROPE, so we cannot definitely reject the null hypothesis. These findings were quite robust across most models, and models incorporating optimistic small effect priors and meta-analytic data were supported by strong evidence, as shown by Bayes factors >10 in most pairwise comparisons with other models, suggesting substantial evidence supporting the benefit of HFNT over COT.

These results should be interpreted in the context of recent observational studies of HFNT in COVID-19-related AHRF which report variable escalation rates, respiratory support strategies, and clinical outcomes across different care pathways (78,79). These studies highlight the heterogeneity of clinical trajectories and management strategies in COVID-19-related AHRF, which should be considered when interpreting the COVID-HIGH findings. In this context, a Bayesian approach helps integrate uncertainty and clinical variability when interpreting treatment effects in practice.

Furthermore, real-world data show an association between positive-pressure non-invasive ventilation and adverse events, such as barotrauma, within the conceptual framework of Patient-Self-Inflicted Lung Injury (P-SILI). Compared with

COT, HFNT is not associated with an increased risk of this complication, making it a particularly attractive technique for use in lower-intensity care settings (78).

Strengths and limitations of this study

The strengths of this reanalysis lie in its comprehensive modelling strategy, inclusion of external evidence, and formal application of Bayesian decision tools such as ROPE and Bayes factors. Moreover, the general strengths of the COVID-HIGH trial, including international recruitment and complete follow-up data, also apply to this analysis. However, this study has several limitations. This was a post hoc re-analysis of the COVID-HIGH trial and was not pre-specified in the original trial protocol. Although all priors were selected based on clinical rationale and external data from existing literature, specifying priors in Bayesian modelling involves a degree of subjectivity, as conclusions depend on both the observed data and the chosen prior distributions. To mitigate this, we explored a wide range of priors, including flat, sceptical, and optimistic priors, as well as one informed by a recent meta-analysis, to assess the consistency and robustness of our findings across varying prior assumptions. Finally, although COVID-HIGH focused on patients with mild hypoxaemia ($\text{PaO}_2/\text{FiO}_2$ 200–300 mmHg), where treatment effects may be smaller and more heterogeneous, the consistency of benefit across our Bayesian models suggests that HFNT may be particularly valuable in settings where the use of noninvasive respiratory support could delay or prevent escalation. The absolute difference in escalation was 6.6%, indicating that for every 15 patients treated with HFNT instead of COT, one patient would avoid escalation. Overall, these findings have important implications for clinicians. They enhance the interpretability of clinical trial data, offering alternative perspectives that closely reflect the natural process of weighing risks and benefits at the bedside, resembling intuitive clinical reasoning,

especially in resource-constrained environments or amid future respiratory pandemics (75).

Finally, this Bayesian reanalysis focused on prespecified clinical outcomes of the original COVID-HIGH trial and should be interpreted within the specific context of patients with COVID-19–related mild AHRF. Future studies should prospectively evaluate the applicability of these findings in other clinical settings and the potential role of dynamic physiological indices, such as the ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate, ROX index, in identifying patients most likely to benefit from HFNT in mild AHRF across different clinical contexts (80).

Conclusions

This Bayesian re-analysis of the COVID-HIGH trial suggests that HFNT likely reduces the need for escalation of respiratory support and promotes timely clinical recovery in patients with COVID-19-pneumonia and mild hypoxaemia, with minimal probability of harm. Uncertainty remains, as the magnitude of this effect was sensitive to prior assumptions and frequently included values compatible with clinically negligible benefit.

LIST OF ABBREVIATIONS

AHRF Acute Hypoxaemic Respiratory Failure

BF Bayes Factor

CI Confidence Interval

COT Conventional Oxygen Therapy

CPAP Continuous Positive Airway Pressure

CrI Credible Interval

FiO₂ Fraction of Inspired Oxygen

HDI 95 % Highest Density Interval

HFNT High-Flow Nasal Therapy

ICU Intensive Care Unit

IMV Invasive Mechanical Ventilation

I² Between-Model Heterogeneity Measure (I-squared)

MCMC Markov Chain Monte Carlo

NIV Noninvasive Ventilation

OR Odds Ratio

PaO₂ Partial Pressure of Arterial Oxygen

PaO₂/FiO₂ Ratio of Arterial Oxygen Partial Pressure to Fraction of Inspired Oxygen

RCT Randomised Controlled Trial

R-hat Gelman–Rubin Convergence Diagnostic Statistic

ROPE Region of Practical Equivalence

RR Risk Ratio

SD Standard Deviation

SpO₂ Peripheral Capillary Oxygen Saturation

DECLARATIONS

Human Ethics and consent to participate

The study protocol of the original COVID-HIGH trial was approved by the Ethics Committee of the coordinating centre (Comitato Etico Catania 1, 01/2021/PO, 25/01/2021) and all participating sites before patient inclusion. The study was performed in accordance with Good Clinical Practice guidelines and ethical principles of the Declaration of Helsinki. The trial was overseen by an oversight committee comprised of independent clinicians with no competing interests. Written informed consent was obtained from all patients or surrogates.

Consent for publication

The patients provided informed consent for inclusion in the COVID-HIGH trial and for the analysis and dissemination of results.

Availability of data and materials

Deidentified participant data are available upon reasonable request. We provided an excerpt of the code for constructing Bayesian linear models in the Supplementary Analysis.

Competing interests

A Ca received consulting fees from Breas, Airliquide, honoraria for lectures or consultancies from Fisher & Paykel, Philips, ResMed, Vitalaire (outside the submitted work). CC participated in an advisory board from Airliquide and received honoraria for lectures from Fisher & Paykel, Philips, ResMed, Vitalaire, and Medicaire (outside the submitted work). CG received honoraria for lectures or consultancies from Vivisol and Air Liquide (outside the submitted work). BE received financial support for attending meetings from Fisher & Paykel. EC received grants from Chiesi

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Figure Legends

Figure 1

Panel A. Components of the Meta-analysis-derived models for the primary outcome. This figure illustrates the elements of the Meta-analysis-derived models on the log-odds ratio scale, featuring the prior distribution (blue line), the likelihood function (green line), and the posterior distribution (red). The black horizontal line highlights the 95% highest density interval (HDI) of the posterior estimate.

Figure 2

Analysis of Posterior Distribution derived from Meta-analysis-derived models for the primary outcome for the primary outcome with the Region of Practical Equivalence (ROPE). The figure shows the Posterior distribution of the log odds ratio, highlighting the proportion of the posterior falling into regions of beneficial (light blue), harmful (light orange), and severe harm (dark orange) effects. The black horizontal line highlights the 95% highest density interval (HDI) of the posterior estimate.

Figure 3

Panel A. Forest plot showing odds ratios (95% credible intervals) for the escalation of the respiratory support outcome under each different prior specification.

Each point represents the posterior median effect size with horizontal lines indicating 95% credible intervals. The vertical dashed red line at $OR = 1$ indicates no effect. Effect sizes are presented on a log scale.

Panel B. Tau vs I^2 curve illustrating the relationship between the between-study heterogeneity parameter (τ) and the I^2 statistic. The vertical red dashed line indicates the posterior median τ value, while the horizontal red dashed line shows the corresponding I^2 value.

Figure 4

Panel A. Forest plot showing odds ratios (95% credible intervals) for the clinical improvement outcome under each different prior specification.

Each point represents the posterior median effect size with horizontal lines indicating 95% credible intervals. The vertical dashed red line at $OR = 1$ indicates no effect. Effect sizes are presented on a log scale.

Panel B. Tau vs I^2 curve illustrating the relationship between the between-study heterogeneity parameter (τ) and the I^2 statistic. The vertical red dashed line indicates the posterior median τ value, while the horizontal red dashed line shows the corresponding I^2 value.

ADDITIONAL INFORMATION

Filename: Additional file 1:

File format: .pdf

Title of data: Supplementary Table 1–2; Supplementary Figure S1–S20.

Contents:

- Excerpt of code for Bayesian analysis models.

- Supplementary Table 1 – Bayesian Model Estimates from brms (Primary Outcome); Supplementary Table 2 – Bayesian Model Estimates from brms (Secondary Outcome).
- Supplementary Figures 1–20, covering: Visualizations of priors, likelihoods, and posteriors under sceptical, optimistic, pessimistic, and meta-analysis priors (Figures S1–S8, S12–S17); Bayes factor heatmaps (Figures S9 and S18); MCMC convergence plots (Figures S10–S11, S19–S20).
- Technical appendix including the COVID-HIGH study protocol and the Statistical Analysis Plan (SAP).

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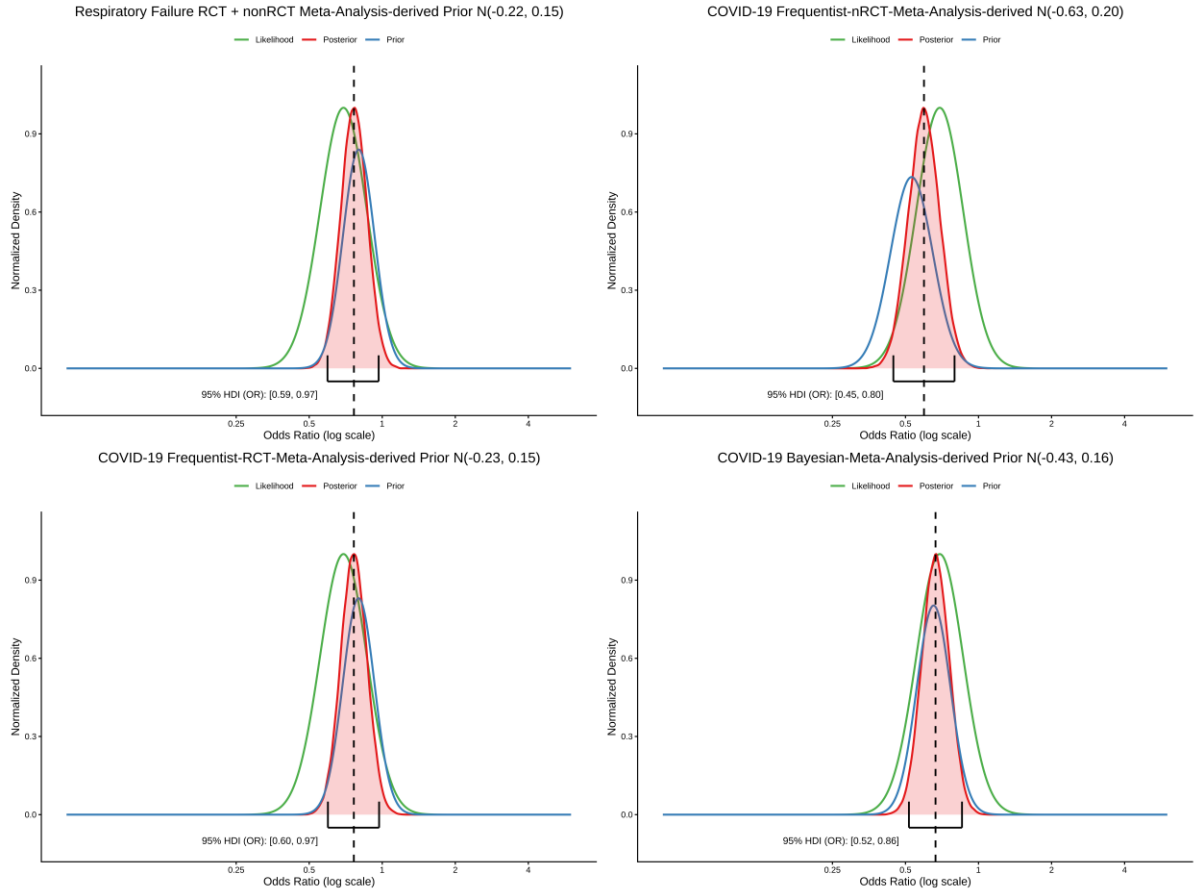
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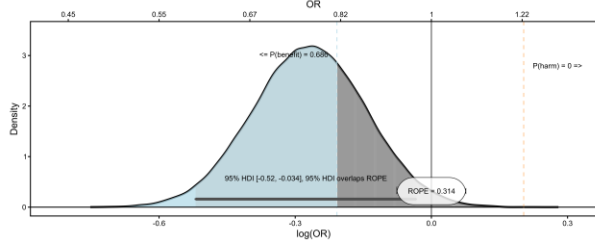
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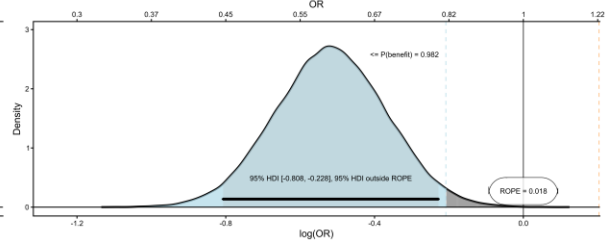


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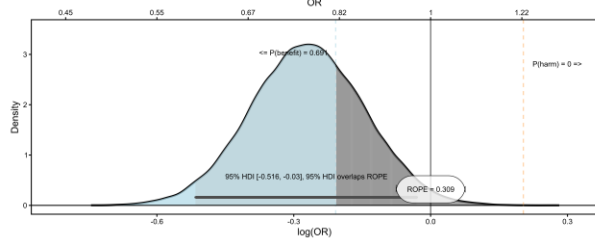
Escalation of Respiratory Support - Probability of benefit by HFNT - Respiratory Failure RCT + nonRCT Meta-Analysis-derived Prior $N(-0.22, 0.15)$



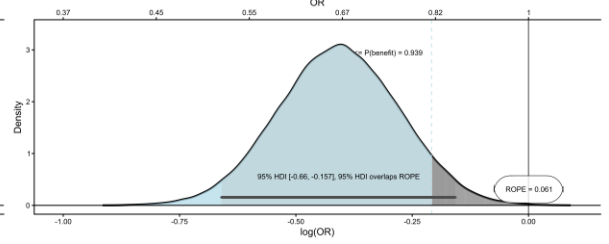
Escalation of Respiratory Support - Probability of benefit by HFNT - COVID-19 Frequentist-RCT-Meta-Analysis-derived Prior $N(-0.63, 0.20)$



Escalation of Respiratory Support - Probability of benefit by HFNT - COVID-19 Frequentist-RCT-Meta-Analysis-derived Prior $N(-0.23, 0.15)$

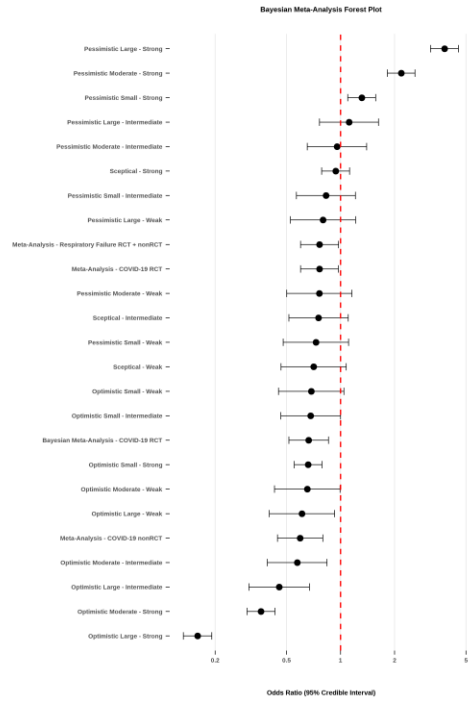


Escalation of Respiratory Support - Probability of benefit by HFNT - COVID-19 Bayesian-Meta-Analysis-derived Prior $N(-0.43, 0.16)$

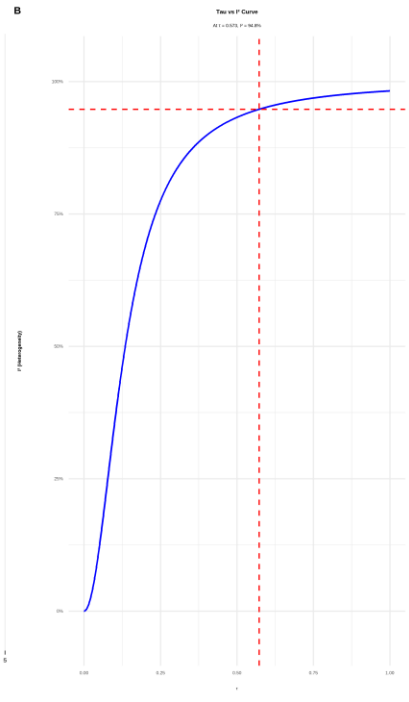


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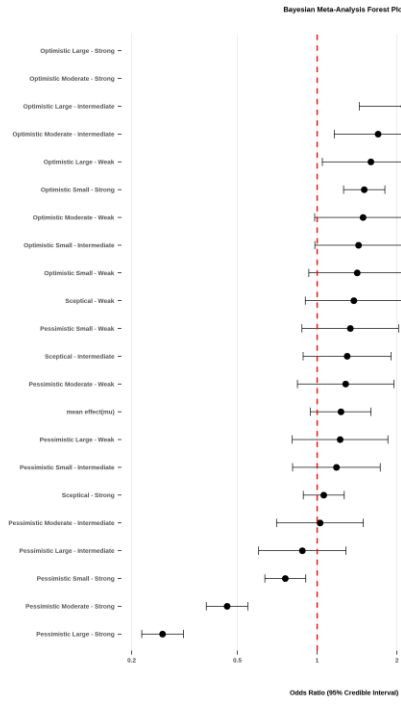


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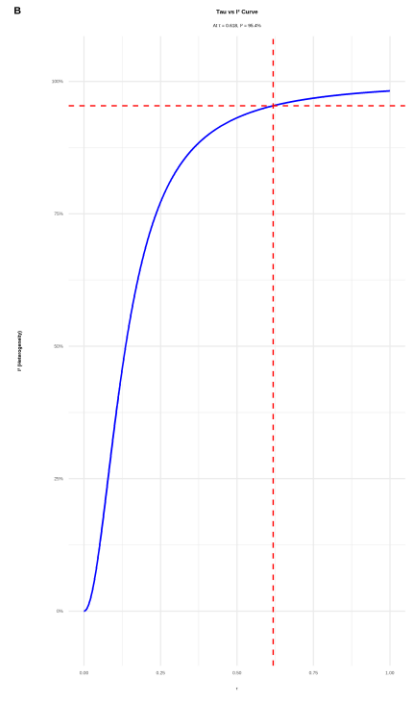


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