infectious disease reports

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Systematic Review

Noninvasive Ventilation Versus High-Flow Nasal Cannula and the Risk of Hospital-Acquired Pneumonia in Acute Respiratory Failure: A Systematic Review and Meta-Analysis

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Abstract

Background/Objectives: To compare the risk of hospital-acquired pneumonia (HAP) in adults with acute respiratory failure treated with noninvasive ventilation (NIV) versus high-flow nasal cannula (HFNC). **Methods:** We prospectively registered the study protocol in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420251173489). We conducted a systematic review and meta-analysis of randomized controlled trials and observational cohort studies comparing NIV and HFNC and reporting HAP. Databases were searched from inception to October 2025. Risk ratios (RRs) were pooled using random-effects models with appropriate variance estimation. **Results:** Seven studies including 3897 patients were analyzed (five randomized trials, $n = 1093$; two observational studies, $n = 2804$). In randomized trials, NIV was not associated with a significant difference in HAP compared with HFNC (RR 1.06, 95% CI 0.81–1.39; $I^2 = 0\%$). Observational studies showed imprecise estimates (RR 1.62, 95% CI 0.00–322,780.06; $I^2 = 51.3\%$). An exploratory analysis combining all studies showed similar results (RR 1.04, 95% CI 0.80–1.34; $I^2 = 0\%$). **Conclusions:** NIV was not associated with a significant difference in the risk of hospital-acquired pneumonia compared with HFNC. Device selection should be guided by clinical factors other than pneumonia risk.

Keywords: hospital-acquired pneumonia; non-invasive mechanical ventilation; high-flow nasal cannula

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Academic Editor: Rok Čivljak

Received: 4 September 2026
Revised: 14 November 2026
Accepted: 18 November 2026
Published: 23 November 2026

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1. Introduction

Hospital-acquired pneumonia (HAP) remains a frequent and clinically relevant complication in patients with acute respiratory failure, particularly in critical care settings. Clinicians associate HAP with prolonged hospitalization, higher resource utilization, and worse outcomes, which makes prevention a central objective during respiratory support management [1,2].

Clinicians widely use noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC) as first-line strategies to avoid invasive mechanical ventilation. Both modalities reduce intubation in selected populations, but they differ substantially in interface, pressure delivery, tolerance, and secretion management [3,4]. These differences raise a clinically relevant question: whether one modality exposes patients to a higher risk of nosocomial pneumonia. Specifically, NIV modalities in patients with high respiratory drive can cause excessive tidal volumes, leading to lung strain and tissue injury. This mechanical damage predisposes lungs to superimposed infections, which may explain the increased hospital-acquired pneumonia risk, prolonged hospital stay, and higher mortality observed in these patients [5].

Although several randomized controlled trials have compared noninvasive ventilation and high-flow nasal cannula in acute respiratory failure, they have consistently focused on respiratory outcomes such as intubation rates and mortality, treating HAP as an underpowered secondary or exploratory endpoint. Furthermore, existing trials exhibit heterogeneous diagnostic definitions for pneumonia and lack standardized reporting of exposure duration, while prior reviews have predominantly pooled disparate respiratory strategies or prioritized non-infectious complications. Consequently, a critical knowledge gap remains: randomized evidence has never systematically synthesized the true comparative risk of HAP between these two modalities [6–9].

We designed this systematic review and meta-analysis to address this gap. We compared the incidence of hospital-acquired pneumonia in adults with acute respiratory failure treated with NIV versus HFNC, with a prespecified focus on randomized evidence.

2. Materials and Methods

2.1. Study Design and Registration

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement [10]. We prospectively registered the study protocol in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420251173489) [11].

2.2. Eligibility Criteria

We included randomized controlled trials and observational cohort studies that enrolled adult patients hospitalized with acute respiratory failure and directly compared noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC).

We considered studies conducted in intensive care units, intermediate care settings, or hospital wards. We excluded studies involving pediatric populations, case reports, case series, narrative reviews, editorials, and conference abstracts without full-text availability. We also excluded studies that did not provide direct comparative data between NIV and HFNC.

2.3. Outcomes

We prespecified hospital-acquired pneumonia incidence, time to HAP onset, and hospital length of stay as primary outcomes, in accordance with the registered protocol.

We evaluated mortality and microbiological findings as secondary outcomes when available. We accepted the definition of hospital-acquired pneumonia as reported in each individual study.

2.4. Search Strategy

We searched PubMed, Scopus, and Web of Science from inception through 26 October 2025, without date restrictions. We restricted inclusion to studies published in English.

We used combinations of controlled vocabulary and free-text terms related to noninvasive ventilation, high-flow nasal cannula, and hospital-acquired pneumonia. We screened reference lists of included studies and relevant reviews, and performed forward citation tracking to identify additional eligible studies. Full search strategies are provided in the Supplementary Materials, Supplementary Table S1.

2.5. Study Selection

Two reviewers independently screened titles and abstracts, followed by full-text assessment for eligibility. The same reviewers independently confirmed study inclusion. Disagreements were resolved through discussion and, when necessary, consultation with a third reviewer.

2.6. Data Extraction

Two reviewers independently extracted data using a standardized data collection form. We extracted information on study design, clinical setting, patient characteristics, respiratory support strategies, and outcome data for all prespecified endpoints. We resolved discrepancies through consensus.

2.7. Risk of Bias Assessment

Two reviewers independently assessed risk of bias. We evaluated randomized trials using the Cochrane Risk of Bias 2 (RoB 2) tool and observational studies using the ROBINS-I tool [12,13]. We resolved disagreements through discussion. We interpreted risk-of-bias assessments within each study design and did not directly compare judgments across tools.

2.8. Statistical Analysis

We calculated risk ratios (RRs) with corresponding 95% confidence intervals (CIs) for dichotomous outcomes. For continuous outcomes, we planned to calculate mean differences or standardized mean differences as appropriate. We conducted meta-analyses using random-effects models, with the restricted maximum likelihood (REML) estimator to calculate between-study variance (τ^2). We applied the Hartung–Knapp adjustment to derive confidence intervals, given the small number of included studies and to improve control of type I error. We assessed statistical heterogeneity using the I^2 statistic and τ^2. We interpreted heterogeneity cautiously, recognizing that low statistical heterogeneity does not exclude the presence of clinical heterogeneity.

We performed prespecified subgroup analyses according to study design (randomized controlled trials vs. observational studies) to account for differences in internal validity and risk of bias. We considered randomized evidence as the primary analysis. We conducted an exploratory analysis combining all study designs to evaluate consistency in the direction and magnitude of effect across evidence sources. We interpreted this analysis as hypothesis-generating. We performed sensitivity analyses using alternative estimators of between-study variance, including the DerSimonian–Laird method, to assess the robustness of the findings. We did not formally assess publication bias due to the small number of included studies (<10), which limits the reliability of funnel plot–based methods [14].

2.9. Certainty of Evidence

We assessed the certainty of evidence for the primary outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias [15].

3. Results

3.1. Study Selection

The database search identified 2242 records (PubMed $n = 339$, Scopus $n = 1450$, Web of Science $n = 453$). After removal of duplicates, 1587 records underwent title and abstract screening. Of these, we assessed 142 articles in full text, and seven studies met all eligibility criteria and were included in the quantitative synthesis (Figure 1).

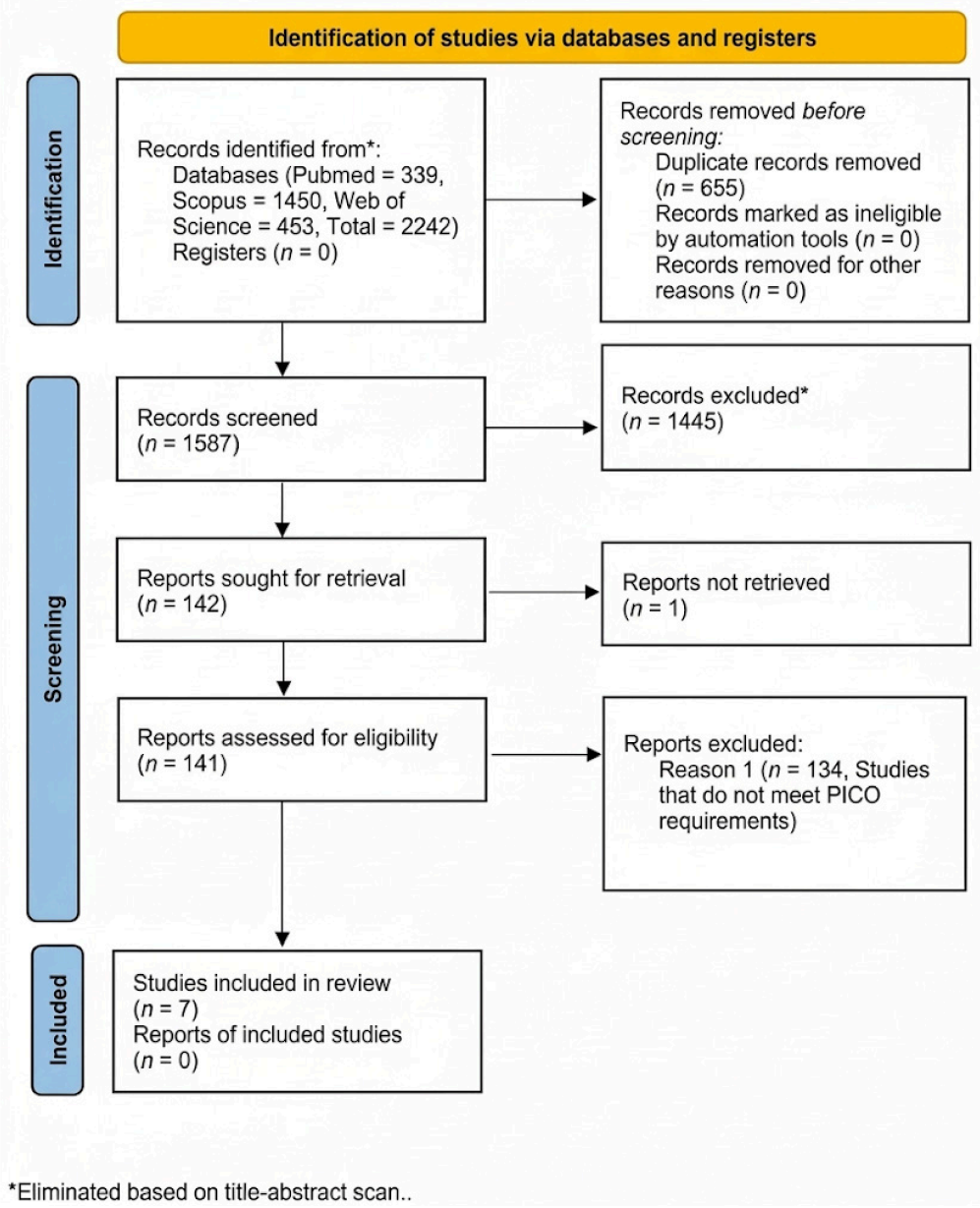

Figure 1. Study selection process. PRISMA flow diagram showing the identification, screening, eligibility, and inclusion of studies evaluating noninvasive ventilation versus high-flow nasal cannula for hospital-acquired pneumonia.

3.2. Study Characteristics

We included seven studies comprising 3897 patients. Five randomized controlled trials enrolled 1093 patients, and two observational cohort studies included 2804 patients.

The randomized trials enrolled clinically heterogeneous populations, including patients with acute hypoxemic respiratory failure, post-extubation respiratory support, exacerbations of chronic obstructive pulmonary disease, obesity at high risk of extubation failure, and

COVID-19–related respiratory failure. The observational studies reflected broader real-world intensive care populations.

Detailed study characteristics, including patient demographics, intervention protocols, and outcome definitions, are summarized in Table 1 and Supplementary Table S2 [4,6,7,16–18].

Table 1. Population characteristics and statistical results of the studies included in the meta-analysis.

Study	Total Population for HAP (*n*)	NIV (*n*)	HAP During NIV (*n*)	HFNC (*n*)	HAP During HFNC (*n*)	Risk of Bias	Log RR	SE	RR
Bouadma L. (2022) [6].	224	109	22	115	21	Low risk	0.1001	0.2742	1.11
Tu G. (2017) [16].	38	18	3	20	0	Serious risk	2.0460	1.4783	7.74
Hernández G. (2025) [7].	144	72	5	72	5	Low risk	0.0000	0.6101	1.00
Frat J. (2019) [17].	313	142	31	171	35	High risk	0.0645	0.2190	1.07
Saunders H. (2023) [5].	2766	2076	46	690	17	Moderate risk	−0.1061	0.2804	0.90
Magdy D. (2023) [18].	230	110	6	120	4	Some concerns	0.4925	0.6319	1.64
Hernández G. (2022) [4]	182	92	4	90	7	Low risk	−0.5816	0.6090	0.56

HAP, hospital-acquired pneumonia; NIV, noninvasive ventilation; HFNC, high-flow nasal cannula; RR, risk ratio; SE, standard error.

3.3. Primary Outcome: Hospital-Acquired Pneumonia

Randomized Controlled Trials

Five randomized trials contributed to the primary analysis. Using a random-effects model with restricted maximum likelihood estimation and Hartung–Knapp adjustment, treatment with noninvasive ventilation was not significantly associated with the risk of hospital-acquired pneumonia compared with high-flow nasal cannula (risk ratio 1.06, 95% confidence interval 0.81–1.39).

We did not detect statistical heterogeneity ($I^2 = 0\%$; $\tau^2 = 0$). The confidence interval excludes large increases or decreases in risk but remains compatible with small effects in either direction. Given the low event rates across studies, any absolute difference between strategies is likely to be small and of limited clinical relevance. Study-level estimates and pooled effects are shown in Figure 2.

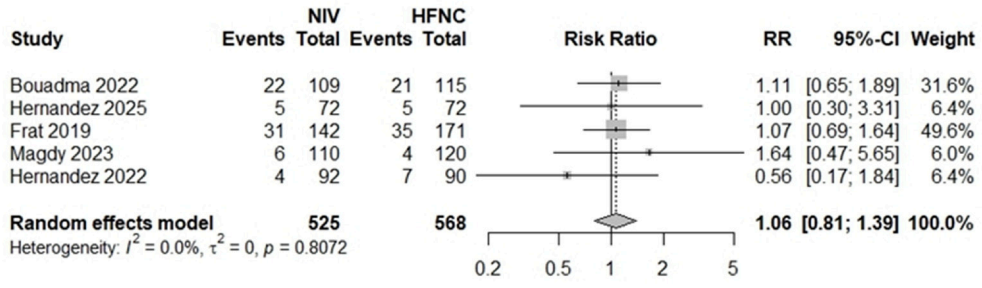

Figure 2. Risk of hospital-acquired pneumonia in randomized controlled trials. Forest plot showing pooled risk ratios (RRs) with 95% confidence intervals comparing noninvasive ventilation and high-flow nasal cannula. We calculated pooled estimates using a random-effects model with restricted maximum likelihood and Hartung–Knapp adjustment. We assessed heterogeneity using the I^2 statistic and between-study variance (τ^2) [4,6,7,17,18].

3.4. Observational Studies

Two observational cohort studies were analyzed separately. Noninvasive ventilation did not significantly change the risk of hospital-acquired pneumonia compared with high-flow nasal cannula (risk ratio 1.62, 95% confidence interval 0.00–322,780.06), with moderate statistical heterogeneity ($I^2 = 51.3\%$). Results are presented in Figure 3.

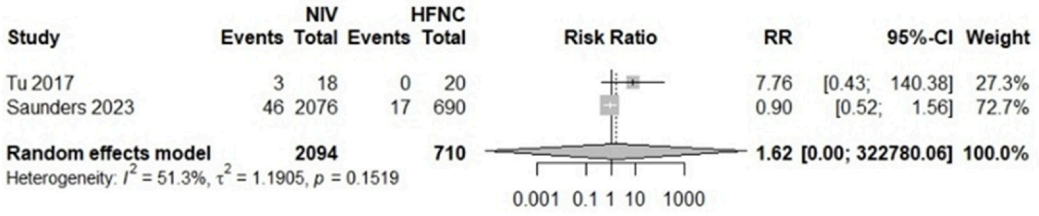

Figure 3. Risk of hospital-acquired pneumonia in observational studies. Forest plot showing pooled risk ratios (RRs) with 95% confidence intervals comparing noninvasive ventilation and high-flow nasal cannula in observational cohort studies. We calculated pooled estimates using a random-effects model with restricted maximum likelihood and Hartung–Knapp adjustment. We assessed heterogeneity using the I^2 statistic and between-study variance (τ^2) [5,16].

3.5. Combined Analysis Across All Study Designs

We performed an exploratory analysis combining all seven studies. Using the same random-effects framework, noninvasive ventilation did not significantly change the risk of hospital-acquired pneumonia compared with high-flow nasal cannula (risk ratio 1.04, 95% confidence interval 0.80–1.34), with no detected heterogeneity ($I^2 = 0\%$; $\tau^2 = 0$). Given differences in study design and risk of bias, we interpret this analysis as supportive of consistency in the direction of effect rather than as confirmatory evidence (Figure 4).

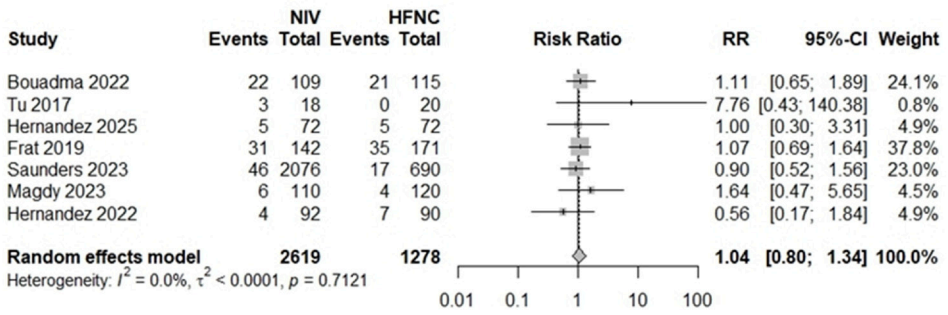

Figure 4. Combined analysis across all study designs. Forest plot showing pooled risk ratios (RRs) with 95% confidence intervals combining randomized controlled trials and observational studies. We calculated pooled estimates using a random-effects model with restricted maximum likelihood and Hartung–Knapp adjustment. We assessed heterogeneity using the I^2 statistic and between-study variance (τ^2). This analysis is exploratory [4–7,16–18].

3.6. Sensitivity Analyses

Sensitivity analyses using alternative estimators of between-study variance, including the DerSimonian–Laird method, yielded results consistent with the primary analysis. The magnitude and direction of the effect remained unchanged across models, supporting the robustness of the findings.

3.7. Additional Outcomes

Data on time to hospital-acquired pneumonia onset, hospital length of stay, mortality, and microbiological findings were limited and inconsistently reported across studies. We

therefore did not perform quantitative synthesis for these outcomes. Available descriptive data are summarized in Table 1 and Supplementary Materials.

3.8. Risk of Bias

Among randomized trials, three studies were judged to be at low risk of bias, one study had some concerns, and one study was rated as high risk of bias. The two observational studies were assessed as having moderate to serious risk of bias. Detailed domain-level assessments are provided in Supplementary Table S3, Supplementary Figures S1 and S2.

3.9. Certainty of Evidence

We rated the certainty of evidence for the primary outcome as moderate according to the GRADE framework, primarily due to imprecision and variability in outcome definitions.

4. Discussion

4.1. Main Findings

In this systematic review and meta-analysis, we found no evidence that noninvasive ventilation meaningfully alters the risk of hospital-acquired pneumonia compared with high-flow nasal cannula in adults with acute respiratory failure. Across randomized trials, the pooled estimate was close to the null effect, with relatively narrow confidence intervals that exclude large, clinically important differences. Observational evidence showed wider and imprecise estimates, but the direction of effect remained consistent with randomized data. The exploratory analysis combining all study designs yielded similar results, reinforcing the overall stability of the findings. Taken together, these results suggest that the choice between NIV and HFNC is unlikely to be a major determinant of hospital-acquired pneumonia risk in this population.

4.2. Interpretation of Findings

The absence of a detectable difference in pneumonia risk between NIV and HFNC challenges mechanistic assumptions that interface-related factors substantially influence infection risk during noninvasive respiratory support. NIV has been hypothesized to increase the risk of microaspiration and secretion retention due to mask interface, intermittent positive pressure, and patient–ventilator asynchrony. In contrast, HFNC provides heated and humidified high-flow oxygen, which may improve mucociliary clearance, reduce airway dryness, and enhance secretion mobilization [19].

Despite these physiological differences, our findings indicate that such mechanisms do not translate into clinically meaningful differences in hospital-acquired pneumonia incidence. One plausible explanation is that pneumonia risk in acute respiratory failure is driven primarily by patient-level factors, including severity of illness, duration of respiratory support, exposure to invasive ventilation, and baseline comorbidities, rather than by the specific noninvasive modality itself [1,2].

Additionally, transitions between respiratory support strategies, particularly escalation to invasive mechanical ventilation, may attenuate any potential differences attributable to the initial modality. Prior randomized trials comparing HFNC and NIV have consistently focused on outcomes such as intubation and mortality rather than infectious complications, and they report similar overall clinical trajectories across modalities [3,6,20].

4.3. Clinical Implications

From a clinical perspective, these findings support the concept of therapeutic equipoise between NIV and HFNC with respect to hospital-acquired pneumonia risk. Clinicians should therefore prioritize other determinants of device selection, including severity of

respiratory failure, work of breathing, patient tolerance, risk of treatment failure, and institutional expertise.

In patients with acute hypoxemic respiratory failure, HFNC has demonstrated advantages in comfort and oxygenation, whereas NIV may provide greater ventilatory support in selected populations, particularly in hypercapnic respiratory failure [3,8]. Current clinical guidelines emphasize individualized selection of noninvasive respiratory support strategies based on physiological and clinical context rather than infection-related outcomes [1,2]. Importantly, the pooled estimates suggest that any true difference in pneumonia risk, if present, is likely to be small and below the threshold of clinical relevance for most patients.

4.4. Heterogeneity and Robustness of Findings

We did not detect statistical heterogeneity in randomized trials or in the combined analysis; however, this should not be interpreted as evidence of clinical homogeneity. The included studies enrolled heterogeneous populations, including post-extubation patients, individuals with chronic obstructive pulmonary disease exacerbations, and patients with COVID-19–related respiratory failure. These populations differ substantially in baseline pneumonia risk, exposure duration, and clinical trajectories.

Furthermore, definitions of hospital-acquired pneumonia varied across studies, reflecting differences in diagnostic criteria and surveillance practices [1,2]. Such variability introduces potential misclassification and may obscure true differences between interventions. The absence of statistical heterogeneity may also reflect limited power to detect between-study variability given the small number of included trials, a well-recognized limitation in meta-analyses of critical care interventions [14].

4.5. Certainty of Evidence

We rated the certainty of evidence for the primary outcome as moderate. Randomized trials provided the most reliable estimates; however, the overall certainty was downgraded due to imprecision and variability in outcome definitions. The relatively small number of studies and events limits confidence in excluding small but potentially clinically relevant differences. Notably, the divergent point estimate observed in the observational subset—specifically in the study by Tu G. et al.—stems from its inclusion of a specialized, highly vulnerable cohort of renal transplant recipients ($n = 38$) under profound immunosuppression, alongside a very small sample size that amplifies random variation [16]. Furthermore, with the exception of the large-scale observational cohort by Saunders et al., the majority of included studies comprised modest sample sizes with low event rates, underscoring the methodological challenge of sparse-data bias in non-randomized comparisons [5]. Observational studies contributed additional context but were affected by moderate to serious risk of bias and substantial imprecision, which reduces their influence on the overall certainty of evidence [15].

4.6. Strengths and Limitations

Prior individual trials comparing NIV and HFNC focused primarily on intubation rates and mortality, treating HAP as a secondary, underpowered endpoint with conflicting or inconclusive secondary signals. The primary contribution of this systematic review is that it bridges this evidentiary gap by pooling disparate randomized data for the first time. Rather than merely echoing individual trial results, our quantitative synthesis provides definitive statistical confirmation that the choice between NIV and HFNC does not meaningfully alter HAP risk across diverse clinical settings, thereby resolving prior uncertainties and supporting clinical equipoise. This study has several strengths. We prospectively registered the protocol, applied rigorous methodology consistent with PRISMA standards, and evaluated

both randomized and observational evidence (Table S4). We performed separate analyses by study design and used contemporary statistical methods, including restricted maximum likelihood estimation and Hartung–Knapp adjustment, which improve the robustness of meta-analytic estimates, particularly in the presence of a small number of studies [14].

However, several limitations should be acknowledged. First, the number of included studies was limited, particularly for observational analyses, resulting in wide confidence intervals and reduced precision. Second, variability in patient populations and definitions of hospital-acquired pneumonia may limit generalizability and introduce measurement bias. Although statistical heterogeneity was low ($I^2 = 0\%$), our review encompasses markedly distinct clinical populations—including COVID-19 acute hypoxemic respiratory failure, post-extubation support, obesity-associated high-risk extubation, and COPD exacerbations. While formal quantitative subgroup analyses by clinical indication were not feasible due to the limited number of studies and low event counts per subgroup, this clinical diversity must be considered when interpreting our findings. Future trials with standardized HAP definitions and dedicated stratification by clinical indication are needed to determine whether specific patient subgroups experience differential infection risks. Incomplete reporting of secondary outcomes precluded quantitative synthesis beyond the primary endpoint. Furthermore, the observational study synthesis demonstrated profound imprecision with an uninterpretable confidence interval spanning several orders of magnitude. This statistical limitation reinforces that observational data in this context offer extremely limited utility for clinical decision-making, underscores the presence of residual confounding in non-randomized designs, and highlights why recommendations must be guided primarily by high-quality randomized evidence. Finally, we did not formally assess publication bias due to the small number of studies, and the possibility of selective reporting cannot be excluded.

5. Conclusions

Current evidence does not demonstrate a significant difference in the risk of hospital-acquired pneumonia between noninvasive ventilation and high-flow nasal cannula in adults with acute respiratory failure. However, given the very small number of HAP events and the overall limited sample sizes across the included studies, these findings must be interpreted with caution. While our results suggest that clinicians may continue to select either modality based on other clinical considerations (such as work of breathing and patient tolerance), large-scale trials specifically powered for infectious complications are required to draw definitive conclusions.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/idr18060136/s1, Table S1: Search strategy; Table S2: Characteristics of studies included in the meta-analysis; Table S3: Risk of bias assessment of included studies; Table S4: Prisma 2020 Checklist; Figure S1: Risk of bias summary, Traffic light plot showing domain-level risk of bias judgments for each included study using RoB 2 (randomized trials) and ROBINS-I (observational studies); Figure S2: Risk of bias graph for all trials (RoB-2 and ROBINS I), Bar plot summarizing the proportion of studies rated as low risk, some concerns, or high/serious risk of bias across each domain.

Author Contributions: All authors have made significant contributions to the conceptualization and design of the work. They have also contributed to the literature review, analysis, and interpretation of the work at various stages. All authors have contributed to the preparation of the draft and its critical review. All authors agree on the final approval of the published version and responsibility for all aspects of the work. Conceptualization: K.B.A., S.A.A., Ş.K. and A.E.; Data curation: K.B.A., S.A.A. and M.S.Ş.; Formal analysis: H.M.A.-O., S.N. and M.S.Ş.; Investigation: H.M.A.-O., K.B.A. and Ş.K.; Methodology: A.E., G.R.C. and S.N.; Project administration: K.B.A. and M.S.Ş.; Supervision: Ş.K. and A.E.; Validation: G.R.C., A.E. and S.N.; Visualization: S.A.A., K.B.A. and H.M.A.-O.; Writing—original

draft: S.A.A.; Writing—review and editing: S.A.A., K.B.A., G.R.C. and A.E. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: An ethics statement is not required. This study is a systematic review of previously published peer-reviewed literature and did not involve the collection of original patient-level data or any direct contact with human participants; institutional ethics committee approval was therefore not applicable. The review protocol was prospectively registered in the International Prospective Register for Systematic Reviews (PROSPERO; CRD420251173489).

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAP	Hospital-Acquired Pneumonia
HFNC	High-Flow Nasal Cannula
NIV	Noninvasive Ventilation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
REML	Restricted Maximum Likelihood
RoB 2	Cochrane Risk of Bias 2 tool
ROBINS-I	Risk Of Bias In Non-randomized Studies—of Interventions
RR	Risk Ratio
τ^2 (Tau-squared)	Between-Study Variance
I^2	I-squared Statistic (Statistical Heterogeneity)

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