Signa Vitae

SYSTEMATIC REVIEW

Antifibrotic therapy in patients with acute lung injury: a systematic review and meta-analysis

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Abstract

Background: Pulmonary fibrosis is a progressive and often irreversible condition that can develop following acute lung injury (ALI), particularly in patients requiring prolonged mechanical ventilation. Antifibrotic agents such as pirfenidone and nintedanib slow fibrosis progression in idiopathic pulmonary fibrosis, but their role in post-ALI fibrosis remains unclear. This meta-analysis aimed to evaluate the effects of antifibrotic therapy on mortality and secondary outcomes in patients with ALI. **Methods**: We searched Embase, PubMed, and Cochrane up to 17 March 2025 for randomized controlled trials and observational studies comparing antifibrotic therapy to standard care in patients with ALI. The primary outcome was all-cause mortality at the longest follow-up available. Secondary outcomes were length of hospital stay and radiological and functional findings. **Results**: We identified six studies (two randomized, two propensity matched and two case control studies) for a total of 697 COVID-19 patients and no study performed on non-COVID-19 patients. Antifibrotic therapy was associated with a significant reduction in all-cause mortality compared to the control group (16.1% *vs.* 23.9%, OR 0.61, 95% CI 0.40–0.93, $p = 0.02$, $I^2 = 40\%$). The number needed to treat to prevent one death was 13. There was no significant difference in length of hospital stay between the antifibrotic and control groups. Individual studies reported improvements in computed tomography severity scores and pulmonary function parameters in the antifibrotic group. **Conclusions**: This meta-analysis suggests that antifibrotic therapy might reduce mortality in patients with ALI. Improvements in radiological and functional outcomes indicate a potential role for antifibrotic agents in modifying disease progression. Further well-designed randomized controlled trials are necessary to confirm these results and determine the optimal use of antifibrotic therapy in post-ALI fibrosis. **The PROSPERO Registration**: The study protocol was prospectively registered in PROSPERO (registration number CRD420251001885).

Keywords

Antifibrotics; Pirfenidone; Nintedanib; Acute respiratory distress syndrome; Acute lung injury; Intensive care unit

1. Background

Pulmonary fibrosis is a progressive and often irreversible condition which leads to respiratory impairment, and which is characterized by excessive deposition of extracellular matrix and damage of lung tissue [1]. Among the available antifibrotic drugs, pirfenidone and nintedanib are the most commonly used agents. Both drugs have been extensively studied and approved for the treatment of idiopathic pulmonary fibrosis and other interstitial lung diseases with progressive fibrotic phenotypes [2].

Pirfenidone exerts its effects by modulating Transforming Growth Factor beta (TGF-β), and platelet-derived growth factor (PDGF) signaling, thereby reducing fibroblast activation and collagen deposition [3]. Nintedanib, on the other hand, inhibits fibroblast proliferation by targeting receptor tyrosine kinases, including vascular endothelial growth factor receptor, fibroblast growth factor and PDGF receptor [4]. These pathways play a crucial role in the development and progression of lung fibrosis, making antifibrotic therapy a key strategy for mitigating fibrotic lung disease [5].

Post-intensive care unit (ICU) pulmonary fibrosis is an increasingly recognized complication following acute lung injury (ALI), particularly in patients requiring prolonged me-

chanical ventilation [6]. The rate of post-ALI fibrosis is significant, with long-term survivors often experiencing persistent pulmonary dysfunction and reduced quality of life [7]. No pharmacological treatments are currently approved to prevent or mitigate fibrosis following ALI. This highlights the urgent need for therapeutic strategies aimed at improving long-term pulmonary function in these patients.

No meta-analysis has systematically evaluated the role of antifibrotic therapy in ALI. Based on the hypothesis that antifibrotic drugs might improve long-term clinical outcomes in ALI survivors, this meta-analysis aims to evaluate the effects of antifibrotic therapy on mortality at the longest follow-up available.

2. Materials and methods

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8] (checklist sees **Supplementary material 1**). The research question was formulated using the Population, Intervention, Comparison, Outcome (PICO) framework: among Intensive Care Unit (ICU) patients with ALI (P), did antifibrotic agents (I), compared to standard care or placebo (C), reduce mortality at longest follow-up available (O)?

2.1 Eligibility criteria

Studies published in peer-reviewed journals comparing antifibrotic agents to standard care or placebo in critical ill settings were included. Both randomized trials and observational studies were considered. Studies with overlapping populations, as well as systematic reviews, narrative reviews, case reports, case series, and editorials were excluded.

2.2 Search strategy

Four researchers independently performed a comprehensive search of PubMed, the Cochrane Central Register of Controlled Trials and Google Scholar, to identify relevant studies from inception until 17 March 2025. Keywords and other free terms (including "pirfenidone", "nintedanib", "intensive care unit") were used with Boolean operators (OR, AND) to construct searches string (**Supplementary material 2**). Conference abstracts obtained from databases and major conference websites were considered eligible. The selection process did not impose limits regarding patient age or the language of publication.

2.3 Study selection

Two authors independently screened titles and abstracts with a standardized form to assess eligibility. A senior investigator resolved any disagreements. Final inclusion was determined after full-text review, with consensus reached among all authors when necessary.

2.4 Data collection

Two independent investigators extracted study characteristics (first author, year of publication, enrollment period, and coun-

try), sample size, setting, and outcomes. Data on drug administration routes and dosage, as well as radiological and functional characteristics, were also collected. In case of missing data on the primary outcome, authors were contacted through email.

2.5 Outcome

The primary outcome was mortality at longest follow up available. Secondary outcomes were length of hospital stay and radiological and functional findings.

2.6 Statistical analysis

For dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method in Review Manager (version 5.4.1; The Cochrane Collaboration, 2020, Copenhagen, Denmark). Continuous outcomes were analyzed as mean differences with 95% CIs using the inverse variance method [9]. When only medians and interquartile ranges (IQRs) were reported, means and standard deviations were estimated using Wan's method [10].

Heterogeneity was assessed with Cochran's Q test, considering $p < 0.05$ as statistically significant. Statistical inconsistency was quantified by Higgins and Thompson's I^2 statistic [11]. I^2 values $< 25\%$, 25–75%, and $> 75\%$ were interpreted as low, moderate, and high inconsistency, respectively. An I^2 $> 50\%$ was regarded as evidence of substantial heterogeneity [12]. A fixed-effect model was applied when heterogeneity was low to moderate ($I^2 < 50\%$), whereas a random-effects model was used for $I^2 > 50\%$ [13]. A two-tailed p-value < 0.05 was considered statistically significant.

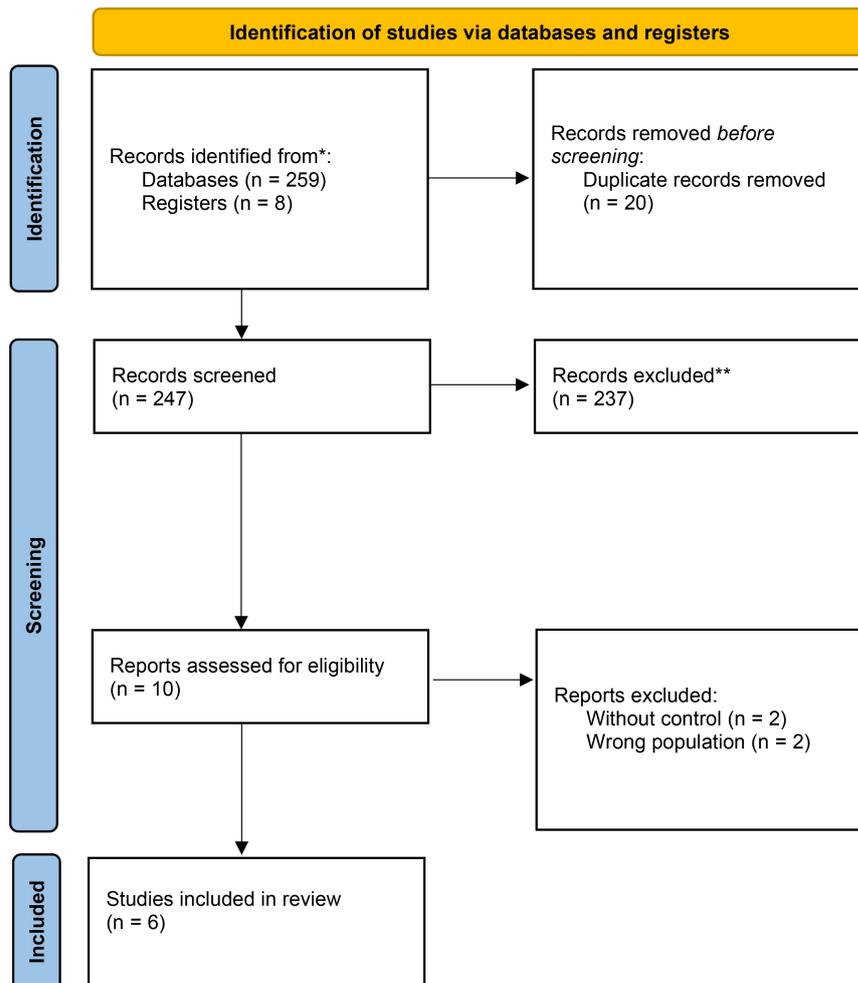### 2.7 Risk-of-bias and quality assessments

Risk of bias (RoB) for each included study was independently assessed by two reviewers using the revised Cochrane RoB 2 tool for randomized trials [14] and the Risk of Bias in Non-randomized Studies (ROBINS) tool for observational research [15]. Any disagreements were resolved in consultation with a third reviewer. A trial was classified as having low RoB only when all domains were rated as low risk.

The certainty of the evidence for the primary outcome was evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [16].

The study protocol was prospectively registered in PROSPERO (registration number CRD420251001885).

3. Results

The search strategy of electronic databases identified 6 studies for a total of 697 patients which met the inclusion criteria and were included in the analyses (Fig. 1). Two studies were randomized [17, 18], two were propensity score matched [19, 20], and two were case control studies [21, 22]. Five studies were conducted in Asia [18–22], and one in Africa [17]. Three studies used pirfenidone as antifibrotic agent [17, 18, 21], two used pirfenidone and nintedanib [19, 22] and one nintedanib alone [19]. Studies were published between

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

F I G U R E 1. PRISMA flow diagram showing literature search results. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

2021 and 2024. In the included studies, the use of concomitant therapies such as antivirals, corticosteroids, and monoclonal antibodies was balanced between the antifibrotic and control groups. An exception was observed in the study by Wang *et al.* [20], where tocilizumab was used in 6% of patients in the antifibrotic group and 0% in the control group, despite propensity score matching. All studies focused on COVID-19 patients. Reasons for exclusions and characteristics of excluded studies are reported in **Supplementary Table 1**.

All the six studies included in the meta-analysis, were at high-risk of bias (**Supplementary Figs. 1,2**). Characteristics of included studies are reported in Table 1 (Ref. [17–22]).

3.1 All-cause mortality at the longest follow-up available

Four studies reported data on the primary outcome for a total of 612 patients showing that patients in the antifibrotic group had reduced all-cause mortality at the longest follow-up available (48/298 (16.1%) *vs.* 75/314 (23.9%), OR 0.61, 95% CI 0.40–

0.93, $p = 0.02$, $I^2 = 40\%$, Fig. 2 with low certainty of evidence, Fig. 3, **Supplementary Fig. 3**, **Supplementary Table 2**). The number needed to treat to prevent one death was 13.

3.2 Length of hospital stay

Three studies reported data on length of hospital stay showing no difference between patients in antifibrotic versus control groups (Mean difference −0.98, 95% CI −7.36 to 5.39 days, $p = 0.57$, $I^2 = 65\%$, Fig. 3).
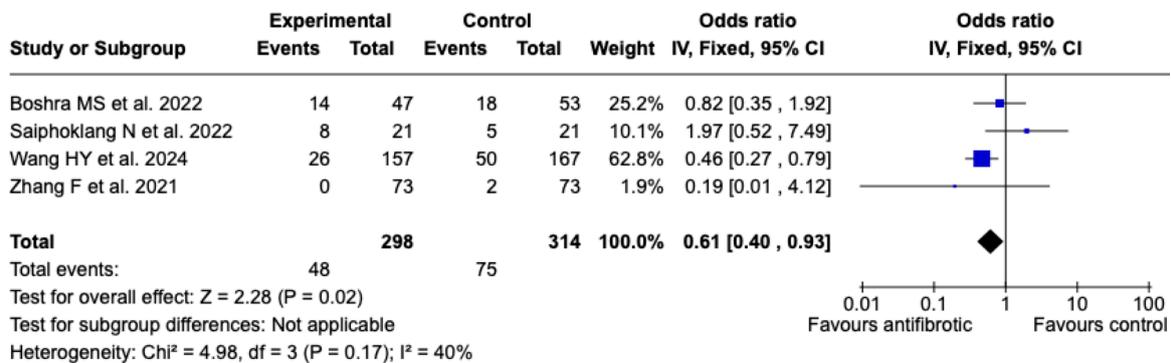
3.3 Radiological and functional findings

The radiological findings identified across studies were not suitable for meta-analysis due to the heterogeneity of reported outcomes. Zhang *et al.* [18] reported a reduction in computer tomography (CT) consolidation scores after one month (0.30 ± 0.65 *vs.* 1.07 ± 1.17, $p = 0.007$). Singh *et al.* [22] reported a reduction in CT severity scores among patients receiving nintedanib, with scores decreasing from 18.14 ± 0.9 at baseline to 3.67 ± 1.21 at 12 weeks. Saiphoklang *et al.* [19]
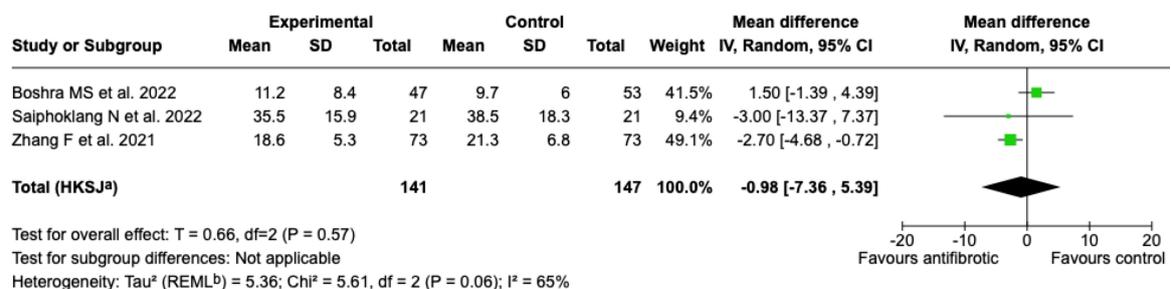
T A B L E 1. Characteristics of the six studies included in the meta-analysis.

Study	Country	Date of enrollment	Design	Type of antifibrotic agent	Follow up	Patients (number)	Dose	Duration
Acat M et al. [21] 2021	Turkey	November 2020–March 2021	Case-control	Pirfenidone	Two months	22	Maximum 2400 mg with weekly dose increase	NR
Boshra MS et al. [17] 2022	Egypt	June 2020–November 2021	Randomized controlled trial	Pirfenidone	Two months	100	Week 1: 600 mg/day Week 2: 1200 mg/day Week 3: 1800 mg/day	3 Week
Saiphoklang N et al. [19] 2022	Thailand	January 2021–January 2022	Propensity score matching	Nintedanib	Two months	42	300 mg/day	At clinician decision
Singh P et al. [22] 2022	India	January 2021–March 2021	Case-control	Pirfenidone or Nintedanib	12-weeks	53	Pirfenidone 1800 mg/day Nintedanib 300 mg/day	NR
Wang HY et al. [20] 2024	Taiwan	June 2019–August 2023	Propensity score matching	Pirfenidone or Nintedanib	1-year	334	NR	NR
Zhang F et al. [18] 2021	China	January 2020–March 2020	Randomized controlled trial	Pirfenidone	4-weeks	143	Week 1: 600 mg/day From week 2: 1200 mg/day	4 weeks

Abbreviation: NR, not reported.

F I G U R E 2. Effect of antifibrotic treatment compared with control on all-cause mortality. IV, Inverse Variance.

F I G U R E 3. Effect of antifibrotic treatment compared with control on length of hospital stay. IV, Inverse Variance.

reported a significant improvement in the peripheral arterial oxygen saturation/inspired fraction of oxygen (SpO_2/FiO_2) ratio in the nintedanib group (144.38 ± 118.05) compared to the control group (55.67 ± 75.09), with a difference of 88.71 (26.66 to 105.76, $p = 0.006$). In the study by Boshra *et al.* [17], patients treated with pirfenidone were more likely to be discharged without progression of lung fibrosis compared to those in the control group (21.3% *vs.* 5.7%; $p = 0.034$) [17]. Furthermore, pulmonary fibrosis involvement of more than 75% on CT scans at discharge was lower in the pirfenidone group compared to the control group (10.6% versus 32.1%, $p = 0.009$) [17]. Acat *et al.* [21] assessed pulmonary function at two months finding that forced expiratory volume in 1 second (FEV_1), ($p = 0.025$), FEV_1% ($p = 0.012$), forced vital capacity (FVC), ($p = 0.026$), and FVC% ($p = 0.017$) were significantly higher in the pirfenidone group than in the control group. Additionally, a significant decrease in pulmonary involvement was observed in CT scans between diagnosis and the second month of treatment in the pirfenidone group ($p < 0.001$) [21].

4. Discussion

We found that antifibrotic therapy was associated with a significant reduction in all-cause mortality at the longest follow-up available. Radiological and functional findings suggested that antifibrotic therapy helped to mitigate disease progression, with improvements in pulmonary function and a reduction in fibrosis.

Previous studies in different clinical settings showed that antifibrotic therapy improved clinical and radiological outcomes in patients with fibrotic lung diseases. In idiopathic pulmonary fibrosis (IPF), pirfenidone and nintedanib slowed disease progression and improved pulmonary function parameters [23]. The findings of our study align with these observations and provide further evidence that antifibrotic agents might have benefits beyond traditional IPF, particularly in patients recovering from severe lung injury.

Pirfenidone has several mechanisms of action, including modulation of cytokine signaling, inflammation, and fibrosis. The effects of pirfenidone on key molecules like TGF-β, Tumor Necrosis Factor (TNF), lipid peroxidation, and apoptosis are of significant interest in understanding its therapeutic effects.

Previous studies demonstrated that pirfenidone inhibits signaling and reduces the expression of TGF-β and TNF expression, preventing inflammation and fibrosis [24–28]. Also, pirfenidone has antioxidant properties and reduces oxidative stress, thereby limiting lipid peroxidation, which is important in preventing the progression of fibrosis and associated tissue damage [29]. Lastly, pirfenidone was found to reduce excessive apoptosis of epithelial cells and to promote the apoptosis of activated fibroblasts [30, 31].

The findings of this study have important implications for clinical practice, critical care management, and future research. Antifibrotic therapy, which were widely used in idiopathic pulmonary fibrosis, may have a role in preventing or limiting fibrosis in patients recovering from prolonged mechanical ventilation, sepsis-induced lung injury, or trauma-related acute lung injury. Given that no approved pharmacological treatments currently exist for preventing post-ALI fibrosis, these results suggest that antifibrotic therapy could be a valuable intervention in ICU survivors, particularly those with high inflammatory burden and prolonged ventilatory support [32].

The mortality reduction associated with antifibrotic therapy also suggests a possible role in improving post-ICU recovery. Pulmonary fibrosis is a major contributor to post-intensive care syndrome, which leads to chronic respiratory impairment, reduced quality of life, and long-term disability [7]. If antifibrotic therapy prevents fibrosis progression, it could reduce the burden of chronic respiratory insufficiency.

The observed improvements in radiological and functional parameters suggest that antifibrotic therapy may help preserve lung function and facilitate pulmonary rehabilitation, potentially reducing long-term disability. If antifibrotic agents limit fibrotic progression, they could lower the burden on rehabilitation programs, decrease the need for long-term oxygen therapy, and improve overall functional recovery in these patients [33].

Post-ALI fibrosis is influenced by several patient-related and treatment-related factors. In elderly individuals, age-related immune dysfunction, including reduced macrophage clearance and persistent inflammation, increase the risk of fibrotic remodeling. Pirfenidone, in addition to its established antifibrotic effects, also possesses anti-inflammatory properties, including modulation of cytokine signaling and reduction of oxidative stress [34]. These mechanisms may be particularly advantageous in elderly ALI survivors. Moreover, mechanical ventilation, although essential for life support, can induce ventilator-associated lung injury through repetitive mechanical stress, further contributing to epithelial damage and fibrosis [35]. These overlapping mechanisms support the rationale for antifibrotic therapy in selected high-risk patients.

Based on the countries and periods of enrollment, the most likely SARS-CoV-2 variants involved in the included studies were the original Wuhan strain in early 2020, followed by Alpha in early-to-mid 2021, Delta during mid-to-late 2021, and Omicron from late 2021 through 2023. Although specific variant identification was not reported in the studies, this temporal distribution should be considered when interpreting the results, as disease severity and fibrotic evolution may vary across variants.

From a healthcare perspective, post-ICU fibrosis is associated with an increased need for hospital readmissions, prolonged outpatient care, and higher healthcare costs [36, 37]. If antifibrotic therapy proves to be effective in reducing fibrosis, it may help decrease healthcare resource utilization by preventing post-discharge complications and reducing the incidence of recurrent respiratory infections. Future studies should explore the economic impact of antifibrotic therapy and assess whether early intervention can provide cost-effective benefits by limiting long-term healthcare expenditures.

This study had several methodological strengths. It was the first meta-analysis to systematically evaluate the impact of antifibrotic therapy on mortality in ALI. The analysis followed PRISMA guidelines and included both randomized and propensity-matched studies, providing a comprehensive assessment of available evidence. Additionally, the protocol was registered in PROSPERO, ensuring methodological trans-

parency.

Despite these strengths, some limitations need to be acknowledged. All included studies had a high risk of bias, as highlighted in the quality assessment. The inclusion of non-randomized studies increased the possibility of confounding factors influencing the results, limiting the ability to draw definitive causal conclusions [38]. There was considerable variability in reported outcomes, particularly in radiological and functional findings, which prevented a quantitative meta-analysis of these parameters. Differences in imaging techniques, lung fibrosis scoring systems, and follow-up durations further contributed to inconsistencies in the data.

The overall sample size remained relatively small, further emphasizing the need for larger, multicenter randomized controlled trials to confirm these findings and establish clear clinical recommendations [39]. Lastly, this analysis is based on COVID-19 related ALI, a condition in which the best treatment is prophylactic vaccination and with an incidence expected to continuously decrease. All studies included in this meta-analysis involved patients with ALI due to SARS-CoV-2 infection. COVID-19-related ALI exhibits a distinct pathophysiology compared to acute respiratory distress syndrome (ARDS) from other causes, such as sepsis or trauma. While fibrotic progression is relatively uncommon in non-COVID ALI, fibrotic lung remodeling appears more frequent following severe COVID-19. In classical ARDS, mortality is often driven by multiorgan failure or secondary infections, and improvements over the past decades have largely resulted from harm-reduction strategies rather than novel pharmacologic interventions [40, 41]. Therefore, our findings primarily apply to COVID-19-related lung injury, and caution is warranted in extrapolating these results to broader ARDS populations. Another limitation is that none of the included studies reported specific details regarding mechanical ventilation settings. Therefore, we cannot confirm whether all patients received lung-protective ventilation strategies, such as low tidal volume ventilation, which could potentially influence the progression of lung injury and the development of fibrosis. Generalizability of these results outside to SARS-CoV-2 disease is unknown, even if common mechanisms in fibrosis were identified across different etiologies of ALI [33].

5. Conclusions

This meta-analysis suggested that antifibrotic therapy reduced mortality in patients with ALI, although further high-quality randomized controlled trials are needed to confirm these findings. The observed benefits in radiological and functional parameters support the potential role of antifibrotic agents in mitigating lung injury following severe respiratory distress. Future research should explore the long-term impact of antifibrotic therapy in post-ALI fibrosis and investigate its role in non-COVID-19 ICU patients at risk of developing progressive pulmonary fibrosis.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

FD, GM, AZ, LB, VA, GP, DO, NDT, LP and CSRG—conceived the study. FD, GM, AZ, NDT, VA, LP, DO and LB—designed the search strategy and did the literature search. GP, CSRG and FD—did the statistical analysis. FD, GM, AZ and LB—wrote the initial protocol. FD, ND, VA, GP, DO, CSRG and LP—wrote the manuscript. All authors shared the study data, gave a critical appraisal of the protocol, provided crucial revisions, and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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Not applicable.

FUNDING

CONFLICT OF INTEREST

The authors declare no conflict of interest. Carolina Soledad Romero Garcia, Laura Pasin, Giacomo Monti are serving as the Editorial Board members of this journal. We declare that Carolina Soledad Romero Garcia, Laura Pasin, Giacomo Monti had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to RJ.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1983098997437284352/attachment/Supplementary%20material.zip.

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