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Respiratory outcomes during the use of the high flow nasal cannula in severe burn patients with inhalation injury: a systematic review

Esiti respiratori durante l'uso della cannula nasale ad alto flusso in pazienti con ustioni gravi e lesioni da inalazione: una revisione sistematica

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ABSTRACT

Introduction: patients with severe burns and inhalation injuries often require mechanical ventilation for life support. High-Flow Nasal Cannulas (HFNCs) represent non-invasive devices that may improve respiratory parameters. However, there is a lack of knowledge on using HFNCs in severe burn populations. The aim of the present work is that of describing the respiratory outcomes in severe burn patients with inhalation injury receiving oxygen therapy via HFNC.
Materials and Methods: a systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Studies focusing on adult patients with severe burns and inhalation injuries treated with HFNC were included; pediatric populations and secondary studies were excluded.
Results: of 796 records screened, three case series and one case report met the inclusion criteria and were included. The findings demonstrated that HFNCs significantly influenced key respiratory outcomes, including improvements in the P/F ratio (PaO_2/FiO_2), reduced respiratory rate, and successful weaning of ventilatory support.
Conclusion: HFNC use appears safe and potentially beneficial for improving gas exchange in severe burn patients with inhalation injuries. However, the overall evidence remains limited. Further research is needed to confirm its efficacy and establish its role in standard burn care.

Key words: burn unit, severe burn patients, high flow nasal cannula, oxygen therapy, inhalation injury.

RIASSUNTO

Introduzione: i pazienti con gravi ustioni e lesioni da inalazione spesso necessitano di ventilazione meccanica per il supporto vitale. Le cannule nasali ad alto flusso (HFNC) sono dispositivi non invasivi che possono migliorare i parametri respiratori. Tuttavia, vi è una mancanza di conoscenze sull'uso delle HFNC nei pazienti con gravi ustioni. Lo scopo del presente lavoro è quello di descrivere i risultati respiratori in pazienti con gravi ustioni e lesioni da inalazione sottoposti a ossigenoterapia tramite HFNC.
Materiali e Metodi: è stata condotta una revisione sistematica seguendo le linee guida Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). Sono stati inclusi studi incentrati su pazienti adulti con gravi ustioni e lesioni da inalazione trattati con HFNC; sono state escluse le popolazioni pediatriche e gli studi secondari.
Risultati: su 796 record esaminati, tre serie di casi e un caso clinico hanno soddisfatto i criteri di inclusione e sono stati inclusi. I risultati hanno dimostrato che le HFNC hanno influenzato in modo significativo i principali esiti respiratori, tra cui il miglioramento del rapporto P/F (PaO_2/FiO_2), la riduzione della frequenza respiratoria e il successo dello svezzamento dal supporto ventilatorio.
Conclusione: l'uso delle HFNC sembra sicuro e potenzialmente benefico per migliorare lo scambio gassoso nei pazienti con ustioni gravi e lesioni da inalazione. Tuttavia, le prove complessive rimangono limitate. Sono necessarie ulteriori ricerche per confermare la loro efficacia e stabilire il loro ruolo nella cura standard delle ustioni.

Parole chiave: unità ustionati, pazienti con ustioni gravi, cannula nasale ad alto flusso, ossigenoterapia, lesioni da inalazione.

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Introduction

Severe burn injuries represent a significant public health burden worldwide, with a disproportionate impact observed in low- and middle-income nations.[1] In the case of patients with serious burns, inhalation injuries are an important factor associated with an increase in morbidity and mortality.[2] It involves thermal or chemical damage of the respiratory tract and the systemic toxicity of gases such as carbon dioxide and hydrogen cyanide.[3] This condition can occur with or without skin burns and can significantly aggravate clinical outcomes.[4]

Inhalation injuries affect both upper and lower airways.[4] Direct thermal damage mainly damages the upper respiratory tract, while chemical irritation caused by smoke and toxic gases can cause inflammation, bronchial paralysis and impaired mucosal clearance in the lower airways.[4,5] These changes increase the risk of obstruction of the airway, infection and hypoxemia.[6] In alveolars, inflammation and surface-removal dysfunction further affect gas exchange and contribute to Acute Respiratory Distress Syndrome (ARDS).[7] Diagnosis is primarily clinical, supported by fiberoptic bronchoscopy, which allows direct visualization of airway damage.[8] Additional tools, such as arterial blood gases and carboxyhemoglobin levels, help assess respiratory function, although no single diagnostic method is definitive.[6,8]

Management focuses on airway protection, adequate oxygenation and complications prevention.[9] Early intubation is often required in patients with facial burns or signs of airway compromise. Narrow-type drugs such as heparin and N-acetylcysteine have shown potential benefits for reducing airway obstruction.[10] In severe cases, Extracorporeal Membrane Oxygenation (ECMO) can be considered.[11,12]

Patients with inhalation injuries show worse results than those with only burns.[13] These patients frequently necessitate prolonged mechanical ventilation and manifest ventilation-related respiratory sequelae, including diminished PaO_2/FiO_2 ratios, elevated serum lactate concentrations, and recurrent desaturation episodes.[14] Clinical markers such as reduced PaO_2/FiO_2 (P/F) ratios, elevated lactate levels, and episodes of desaturation are associated with poor prognosis.[14,15] Long-term complications include restrictive lung diseases, reduced exercise tolerance, and impairment of the quality of life.[16] Cognitive and psychological disorders are also more common and are likely related to hypoxia, prolonged stay in the Intensive Care Unit (ICU) and the use of sedatives.[17]

Due to the severity of their condition, the majority of these patients require management in specialized units, with intensive monitoring and support.[18] Inhalation injury refers to damage to the airways resulting from the inhalation of hot air, smoke, toxic gases, steam, combustible vapors, or particulate matter into the mouth, nose, throat, and trachea.[19] It is estimated that approximately 10-20% of burn patients also sustain inhalation injury, which has been recognized as an independent predictor of mortality in many epidemiological studies on burn injuries.[20,21] Shock remains the leading cause of death during the acute resuscitation phase, with the majority of fatalities occurring within the first 72 hours post-injury.[22] Mechanical ventilation is the cornerstone of respiratory support for burn patients with inhalation injuries.[23]

Ventilation strategies for respiratory dysfunction in critically ill patients, including those with severe burns, remain an evolving area of research.[24] While mechanical ventilation is considered life-saving for these patients, it is associated with several adverse effects, such as prolonged hospital stays and increased costs.[6] High-Flow Nasal Cannulas (HFNCs) have emerged as a viable alternative for patients who do not require extensive ventilatory support.[25] The advantages of this approach have been well-documented in the literature, including more stable FiO_2 levels, higher flow rates, decreased air resistance, and enhanced delivery of warm, adequately humidified air, all of which contribute to improved alveolar ventilation.[26] Additionally, HFNCs have improved the P/F ratio and reduced respiratory rate in critical patients.[27]

In contrast to conventional oxygen therapy, which utilizes lower flow rates and non-humidified gases, HFNC therapy consists of several key components.[25,26] These include a flow generator that delivers gas flow rates up to 60 liters per minute, an air-oxygen blender that adjusts the FIO_2 from 21% to 100% regardless of the flow rate, and a humidifier that saturates the gas mixture to a temperature range of 31°C to 37°C.[28] The heated, humidified gas is delivered to a wide-bore nasal tip through heated tubing to prevent condensation.[25,26] Although several studies have investigated invasive ventilatory strategies in patients with severe burns, data on the use of HFNC in patients with severe burns with inhalation injuries remain lacking. The efficacy of HFNC in improving respiratory function and reducing pressure-related complications is well-documented in other clinical contexts. Moreover, as a non-invasive modality, HFNC may reduce the risk of airway-associated infections in severe burn patients. This review aims to address this gap by synthesizing the available evidence on respiratory outcomes in severe burn patients with inhalation injuries managed with HFNC.

Aim

The objective of this review is to summarize and describe the respiratory outcomes in severe burn patients with inhalation injuries treated with HFNC therapy.

Materials and Methods

This systematic review was conducted in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29]

Eligibility criteria

To be included in this review, studies had to be i) primary research, ii) published in peer-reviewed journals, iii) written in English or Italian, iv) focused on adult patients with inhalation injuries in severe burn patients (acute and post), and v) reporting on HFNC use. No publication date limits were imposed. Exclusion comprised secondary research (*e.g.*, reviews), unpublished studies (*e.g.* grey literature), and not peer-reviewed studies. Records in languages other than English or Italian were omitted due to translation limitations. Studies involving adolescent patients, post-operative patients without burn injuries or inhalation injury, hospital stays shorter than 48 hours, or the use of respiratory support other than HFNC *e.g.*, low-flow nasal cannulas, face masks, continuous or bilevel positive airway pressure) were also excluded.

Search strategy

A comprehensive search was performed in January 2025 across PubMed (via MEDLINE), Scopus, CINAHL (via EBSCO), and Web of Science (via EBSCO). Guided by the Population Intervention Outcome (PIO) framework[30], the search targeted adult burn patients with inhalation injuries in severe burn patients (acute and post) (population), the use of HFNCs (intervention), and the effects on P/F ratio, lactate levels, desaturation, and respiratory wearing (outcomes). No comparator was included. Search terms combined free-text keywords, controlled vocabulary (*e.g.*, MeSH), and Boolean operators (*e.g.*, AND/OR). No filters were applied. Full search strategies for PubMed are reported in the *Supplementary Materials, Table 1.*

Study selection

The screening process consisted of two main phases: abstract and title screening, and full-text screening. All retrieved records were imported into Zotero© for duplicate removal via automated and manual checks. The remaining records were uploaded to Rayyan© for screening[31], conducted by two independent reviewers (LC and FL) based on the eligibility criteria. A third researcher not involved in the selection process (FG) uploaded the records and served as a mediator if disagreements in selection occurred.

Eligible studies from the initial title/abstract screening underwent full-text assessment, using institutional resources and online searches to obtain complete articles.

Data extraction

Following the Cochrane Handbook for Systematic Reviews[32] guidelines, data were extracted using a customized charting template in Microsoft Excel©. Two reviewers (LC and FL) independently recorded study characteristics (*e.g.*, authors, year, design, setting, population, outcomes), outcomes direction (positive, neutral, negative), and key findings.[33] Discrepancies were resolved through discussion with a third researcher (FG).

Risk of bias assessment

Two reviewers (LC and FL) appraised each study using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists[35]. Checklist items were scored as Yes (Y), No (N), Unclear (U), or Not Applicable (NA), with a maximum of ten points for case series and eight points for case reports. Studies were categorized by overall percentage scores as high (<50%), moderate (50-70%), or low (>70%) risk of bias. Conflicts were addressed by consultation with a third researcher (FG). The quality level of the included studies was categorized based on the scores assigned to individual items representing the outcome assessment criteria of the JBI checklists.[34]

Effect measures and synthesis methods

Quantitative outcomes (*e.g.*, means, standard deviations, odds ratios, correlation coefficients). According to the last edition of the Cochrane Handbook for Systematic Review,[32] due to methodological heterogeneity, a meta-analysis was not feasible. Instead, a narrative synthesis was performed following Synthesis Without Meta-analysis (SWiM) guidelines.[35] A vote-counting method categorized effects as positive (+), negative (−), or non-significant (0), to indicate improved, worsened, or unchanged outcomes using HFNC. Multiple effects from a single study were counted individually. Levels of evidence were determined according to the Oxford Centre for Evidence-Based Medicine tool (OCEBM).[29] Finally, a Harvest plot[36] visualized effect directions, sample sizes, and p-values, adhering to Cochrane recommendations.[29,32]

Outcome

Target outcomes were selected based on existing literature: i) P/F ratio (PaO_2/FiO_2), with lower values indicating impaired oxygenation and potential inhalation injury;[37] ii) lactate levels, as hyperlactatemia may reflect reduced tissue perfusion and risk of complications such as sepsis in severe burn patient;[38] iii) oxygen desaturation (SpO_2), as an indicator of hypoxia and airway compromise;[39] and iv) respiratory fatigue, suggestive of increased work of breathing and weaning difficulties.[37]

Results

Study selection

The initial search identified 796 potentially relevant articles. After removing duplicates (n=61), records remained and were screened based on their titles and abstracts (n=735). Following this screening phase, potentially relevant records (n=28) proceeded to full-text evaluation. All full texts were retrieved. During the full-text screening, 24 records did not meet the eligibility criteria and were excluded. Therefore, a total of 4 studies were included in this review (Figure 1).

Study characteristics

The included studies were published between 2023 and 2024,[40-43] comprising three case series[40-42] and one case report conducted in Italy[43] and Turkey.[40] A total of 30 severe burn patients were included in these studies. The overall sample was predominantly composed of males (n=17, 56.6%) and ranged from 28 to 65 years. The total body surface area burn size compromised ranged from 25% to 60%. In two studies, the body mass index was considered and ranged from 22-40.3.[41,42] Only one study considered the ASA score, which reported the predominance of the level 3 score.[41] More details are provided in Table 1.

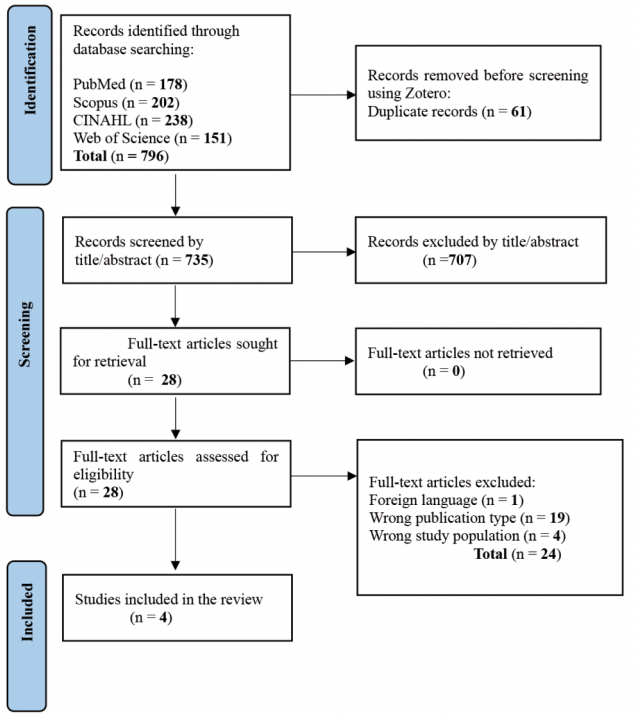


Figure 1. PRISMA flowchart reports the records screening procedure, the number of sources included and excluded, and the reasons.

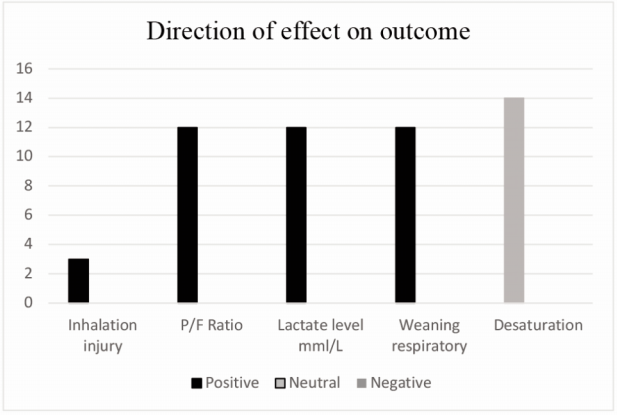


Figure 2. Harvest plot of studies included.

Table 1. Characteristics of sources of evidence.

Authors and years	Study design	Country	Setting	Sample	Intervention	Sensitive outcome	Direction of association	Levels of evidence	Main findings
Akın *et al.*, 2024	Case series	Turkey	Burn Treatment Unit	3	Use of High flow nasal cannula after major burns	Inhalation injury	+	4	One patient, a 29-year-old male with 35% TBSA burns, received HFNO treatment for inhalation injury on the sixth day after the trauma. After 72 hours of HFNO application, the patient's pulmonary symptoms improved. The second patient had 60% TBSA burns and developed respiratory distress symptoms on the fifth day after the trauma. After 7 days of HFNO application, all symptoms and findings of ARDS were resolved. HFNO has been used for treating ARDS related to major burns (60% of burned TBSA) in a 28-year-old patient, and improvement was achieved. The use of HFNO in pul monary insufficiency among burn patients has not been reported previously.
Coletta *et al.*,2023	Case series	Italy	Burn Intensive Care Unit	12	Use of High flow nasal cannula after major burns	P/F ratio Lactate mml/L	+ + Weaning respiratory	4 +	After protracted MV, the P/F ratio of all patients increased (mean 369.33 ± 44.62, min 296, max 440, median 370). At the time of extubation, shortly before starting treatment with HFNC, the mean P/F ratio was 292.58 ± 41.25 (min 210, max 380, median 304). After 48 hours of oxygen therapy, patients showed a remarkable increase in P/F ratio compared with the beginning of therapy, with a mean of 379.33 ± 31.56 (min 302, max 406, median 392.5)
Coletta *et al.*,2024	Case series	Italy	Burn Intensive Care Unit	14	Use of flow nasal cannula during enzymatic debridement procedures under deep sedation	Desaturation <90%	-	4	In only two cases, desaturation events were identified when the SpO_2 value dropped below 90%, respectively, for 3 and 4 seconds. These events promptly subsided with the jaw thrust manoeuvre. 64.3% achieved a RASS of -5, while 35.7% a RASS of -4
Rinaldi *et al*. 2024	Case report	Italy	Burn Intensive Care Unit	1	HFNC preoxygenation for predicted difficult airway	Desaturation	0	4	A high-flow nasal cannula is safe during pre-oxygenation procdures under analgesia for video laryngoscopy.

ARDS, Acute respiratory distress syndrome; TBSA, Total body surface area; HFNO, High-Flow Nasal Oxygen; HFNC, High flow Nasal Cannula. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence: Level 1=Systematic review of randomized trials; Level 2=Randomized trial; Level 3=Non -randomized controlled cohort/follow-up study; Level 4=Case-series, case-control, or historically controlled studies; Level 5=Mechanism-based reasoning. Direction of Association (Campbell *et al.*, 2020): A significant positive association between HFNC and the investigated outcome(s) was denoted by a plus sign (+); Significant negative association between HFNC and the investigated outcome(s) was denoted by a minus sign (–); non-significant association between HFNC and the investigated outcome(s) was denoted as 0.

Study quality assessment and quality of evidence

The quality assessment of the studies reported a score between 62.5% to 70%[40-43] (Table 2). According to the JBI score, three included studies were rated as having moderate quality,[41-43] while only one reported high quality.[40] In the three included case series, it was unclear whether the subjects were included consecutively and if the inclusion was completed. The evidence reported by the included studies is level 4, according to the OCEBM score (Table 1).

Synthesis of findings

Two case series describe using HFNCs when treating major burn patients.[40,41] One case series reported using HFNC during enzymatic debridement procedures under deep sedation,[41] while one report showed that HFNC could be used during preoxygenation for predicted difficult airway.[43] The included studies describe respiratory outcomes such as inhalation injury, PaO_2/FiO_2 ratio, lactate levels, respiratory weaning, and episodes of desaturation (SpO_2<90%) in severe burn patients treated with HFNC[40-43] (Figure 2).

A case series reported the benefits of using HFNC on respiratory parameters such as respiratory rate [start treatment (28-31/min); end treatment (14-16/min)], p_{O2} [start treatment (40 mmHg); end treatment (98 mmHg)], SpO_2 [start treatment (78%); end treatment (99.3%)].[40] Similarly, in the second burn patient, a positive impact of the use of HFNC was observed in the respiratory rate [start treatment (30-35/min); end treatment (15-17/min)], p_{O2} [start treatment (68.7 mmHg); end treatment (95 mmHg), SpO_2 [start treatment (78%); end treatment (98.4%)].[40] In the third burn patient, respiratory parameters were positively influenced by HFNC, such as respiratory rate [start treatment (28-30/min); end treatment (16-18/min)], p_{O2} [start treatment (36.7 mmHg); end treatment (69.2 mmHg)], SpO_2 [start treatment (74.7%); end treatment (94.4%).[40] Coletta *et al.* reported a series of cases in which marked oxygen saturation episodes occurred in patients with critical burns receiving a HFNC while under deep sedation for enzymatic bromelain degradation; each episode resolved quickly after the use of the jaw-thrust technique, indicating a negative association with HFNC (Figure 2).[41]

One case series reported the improvement of respiratory parameters during treatment with the HFNC. In fact, after monitoring at 3, 6, and 48 hours post-extubation, major burn patients showed an improvement of P/F ratio at 48 h [in extubation (mean=292.5, SD=41.2), vs after 48 h (mean=379.3, SD=31.5)]; furthermore, the authors noted that lactate levels did not rise appreciably during oxygen delivery via HFNC: 48 h after extubation, mean lactate was 1.4 mmol/L (SD 0.5) while patients were still on mechanical ventilation, compared with 1.1 mmol/L (SD 0.3) during HFNC therapy with a positive effect on lactate reduction (Figure 2).[42] A case report describes the successful airway management of a 73-year-old woman with post-burn mentosternal scar contracture using a combined awake videolaryngoscopy and fiberoptic bronchoscopy approach. Preoxygenation at FiO2-100% and a flow of 60 l/min with HFNC ensured optimal oxygenation and patient comfort during the awake intubation process.[43]

Discussion

The aim of this review is to provide a descriptive synthesis of respiratory outcomes in severe burn patients with inhalation injuries managed with HFNC therapy. The main findings of the study show that the use of HFNC has had a beneficial effect, as shown by an increase in the P/F ratio, a reduction in the lactate level (mmol/L) and an improved respiratory weaning. The results obtained from this review are consistent with the existing literature on the severe burn patient.[44]

Inhalation injury remains a leading concern in burn care, and its incidence increases with burn severity and advancing patient age.[8] When burns are moderate to severe and inhalation injury is suspected, monitoring carboxyhemoglobin (COHb) levels is critical, and high-flow oxygen therapy should be initiated until carbon monoxide toxicity is excluded.[8] In a pilot study involving two cohorts (no-HFNC, N=5; HFNC, N=3), Gavelli and colleagues showed that high-flow nasal cannula therapy hastened the decline of carboxyhaemoglobin in acute carbon-monoxide poisoning relative to standard treatment, indicating that HFNC could assume a broader role in the management of inhalation injuries.[45] Inhalation injury is recognized as a risk factor for prolonged mechanical ventilation.[46] Moreover, prolonged mechanical ventilation is often required in severe burn patients, and improvements in the PaO_2/FiO_2 ratio correlate with reduced ventilation durations.[47,48] In the studies reviewed, HFNC use was linked to favorable changes in this ratio.[27] Early-phase oxygenation deficits in severe burn patients are frequently attributed to upper airway obstruction,[49] although this risk is typically lower within 12 hours of the injuries.[50] While these observations are promising, caution is warranted given the predominantly descriptive nature of the evidence.

Future research should carefully assess whether invasive ventilation can be fully prevented in carefully selected critically ill burn patients, especially patients with simultaneous inhalation injuries. To determine safety thresholds, physiological predictors of success, and long-term lung effects, prospective multi-centre studies are needed to compare high-flow nasal oxygen, non-invasive ventilation, and hybrid breathing protocols with conventional breathing protocols. Integrating real-time lung mechanical monitoring, biological markers for lung injury and adaptive retraining algorithms can finally identify subgroups of patients for which the elimination of invasive ventilation results in superior survival and functional recovery.

Table 2. Quality appraisal of studies included.

Checklist for Case Series Critical Appraisal tools for use in JBI Systematic Reviews												
Authors and years	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Result (n, %)	Level of Quality
Akın *et al.*, 2024	Y	Y	Y	U	U	Y	Y	Y	Y	U	(7, 70%)	HIGH
Coletta *et al.*, 2023	Y	Y	Y	U	U	Y	U	Y	Y	U	(6, 60%)	MODERATE
Coletta *et al.*, 2024	Y	Y	Y	U	U	Y	U	Y	Y	U	(6, 60%)	MODERATE

Checklist for Case Series Critical Appraisal tools for use in JBI Systematic Reviews										
Authors and years	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Result (n, %)	Level of Quality
Rinaldi *et al.* 2024	Y	Y	U	Y	U	Y	U	Y	(5, 62.5%)	MODERATE

Checklist for Case Series and Case report in Critical Appraisal tools, JBI=Joanna Briggs Institute. Y=Yes, N=NO, N/A=Not Applicable, U=Unclair. Level of Quality (Y); Low<50%; Moderate 50%=> and <70%; High >=70%

Implications of clinical practice

HFNCs offer several potential advantages in burn intensive care settings. By providing a stable fraction of inspired oxygen (FiO_2) and high flow rates, HFNCs can enhance oxygen delivery while reducing inspiratory resistance. Additionally, delivering warmed and humidified oxygen may be particularly beneficial for patients with inhalation injuries, as it helps prevent airway dehydration and supports mucociliary clearance.[51]

In burn-injured patients, the duration of mechanical ventilation is usually significantly longer than the general intensive care population. This long ventilation requirement reflects the combined burden of inhalation injuries, systemic hypermetabolism and frequent infectious complications. Consequently, evidence-based strategies targeted at both a delay in the initiation of invasive ventilation, if rigorous non-invasive support is possible, and an accelerated, protocolized ventilation have emerged as crucial clinical priorities, resulting in a reduction in ventilator-related lung injuries, airway morbidity and overall ICU stay time.

Limitations

This review has several limitations. First, the number of studies specifically investigating HFNC in burned patients with respiratory dysfunction is limited, raising concerns about the applicability of findings drawn from broader intensive care populations. Additionally, included studies employed care reports or case series designs, introducing a risk of selection bias and limiting the overall strength of the evidence. Given the substantial heterogeneity in study populations, HFNC protocols, outcome measures, and the descriptive nature of the included study designs (case reports and case series), a meta-analysis could not be performed, necessitating the adoption of a narrative synthesis approach, as reported in previous studies.[52,53] Finally, restricting inclusion to English or Italian publications may have excluded relevant data from other regions.

Conclusions

In conclusion, this review underscores the potential benefits of HFNC therapy for adult patients with severe burns, particularly regarding improved respiratory outcomes. Although the included studies indicated a positive impact on oxygenation parameters and weaning success, the overall level of evidence remains moderate (OCEBM level 4). Consequently, caution is advised in generalizing these findings. Notably, no previous review has focused on the respiratory outcomes of HFNC in this population. Further high-quality research, including randomized clinical trials, is essential to confirm HFNC's efficacy, minimize device-related complications, and optimize treatment protocols for severely burned patients.

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Online supplementary materials

Table 1. Search strategy in PubMed and final search strings for each database.

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