

SYSTEMATIC REVIEW & META-ANALYSIS

Fire-Related Smoke Inhalation Injury as an Independent Predictor of Mortality in Hospitalized Burn Patients: A Systematic Review and Meta-Analysis of Adjusted Estimates

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ABSTRACT

Background: Smoke inhalation injury is the main fire-related respiratory injury in burn patients and is included in most burn mortality scores, but whether it predicts death independently of burn size and age has been disputed.

Objective: To estimate the multivariable-adjusted association between inhalation injury and mortality in hospitalized burn patients and the attenuation produced by adjustment.

Methods: PubMed, Europe PMC, OpenAlex and Scopus were searched without date or language limits, with citation searching. Cohort studies reporting an adjusted estimate for inhalation injury were included. Adjusted odds ratios (ORs) were pooled with random-effects models (DerSimonian-Laird, Hartung-Knapp); risk of bias was assessed with the Quality In Prognosis Studies (QUIPS) tool and certainty with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The protocol was not registered.

Results: 53 cohorts (338,479 patients, 28 countries) were included. The pooled adjusted OR from 44 cohorts was 3.23 (95% confidence interval [CI] 2.67–3.90) (I^2 72.3%; 95% prediction interval 1.43–7.30); adjusted hazard ratios gave 2.46 (1.45–4.19) (7 cohorts). The crude OR was 9.45 (6.40–13.95). In 23 cohorts reporting both, adjustment reduced the OR from 9.61 to 2.92. Estimates were similar in high-income (3.20) and low- and middle-income countries (3.38; $p = 0.76$). No small-study effects were found (Egger $p = 0.93$); certainty was moderate.

Conclusion: Inhalation injury was associated with about threefold higher adjusted odds of death after burns, a smaller association than crude comparisons suggest. It should remain a core element of early burn triage and risk adjustment, including where bronchoscopic confirmation is unavailable.

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1. Introduction

Burns remain a major cause of injury-related death and disability. The Global Burden of Disease Study estimated more than eight million burn injuries worldwide in 2019.^{1–3} Since 1990, age-standardized incidence and death rates have fallen. Death rates still vary inversely with the socio-demographic index,^{1,2} but the burden attributed to inhalation injury showed no such gradient.³ Projections point to a continued rise in burn injuries and burn-related disability-adjusted life years until 2050.⁴ Survival after a given injury depends strongly on a country's economic status. Access to surgical burn care matters as well.^{5,6}

Fire-related respiratory injury covers a spectrum. At one end, entire populations in Indonesia and neighboring countries are exposed to haze from peatland and forest fires, and respiratory consultations and hospitalizations rise measurably.^{7,8} At the other end lies smoke inhalation injury in patients with cutaneous burns, which carries the highest case fatality and is the subject of this review. Emergency physicians, internists, pulmonologists and intensivists often assess and resuscitate these patients first, many of them outside burn centers. The prognostic weight of inhalation injury therefore matters well beyond burn surgery, and that is why it deserves a precise estimate.

Inhalation injury has three components: thermal damage to the upper airway, chemical injury of the tracheobronchial tree and alveoli from combustion products, and systemic toxicity from carbon monoxide and cyanide. It is linked to early endotheliopathy and abnormal fibrinolysis,^{9,10} to greater fluid retention during resuscitation,¹¹ and to higher rates of pneumonia, ventilator-associated pneumonia and acute respiratory distress syndrome (ARDS). Oxygenation is also worse when ARDS develops.^{12–15} Diagnosis, however, remains imprecise. Bronchoscopic grading has limited inter-rater reliability. Repeat examinations add little prognostic information.^{16,17} Clinical signs predict bronchoscopic findings and the need for intubation only imperfectly, which has prompted multivariable and machine-learning prediction models.^{18–20} An international expert panel agreed with most published recommendations but stayed uncertain about bronchoscopy-guided resuscitation, ventilation modes and nebulized therapies.²¹ Treatment evidence is thin. Nebulized heparin with or without N-acetylcysteine, hydroxocobalamin for suspected cyanide toxicity and early tracheostomy are all still under evaluation.^{22–25}

The revised Baux score and most burn mortality models include inhalation injury because of its presumed prognostic weight. These models continue to be validated and recalibrated in high-income and resource-limited settings.^{26–29} Yet the evidence for an independent effect is weaker than this routine use suggests. Recent syntheses covered only

parts of the question. One meta-analysis was restricted to children and relied mainly on case-control studies.³⁰ Another pooled risk ratios for several predictors of death in older adults.³¹ Two reviews examined only bronchoscopic severity grades in patients who all had inhalation injury.^{32,33} None pooled multivariable-adjusted estimates across all age groups and income settings. Bronchoscopy is rarely available in much of Indonesia, so the diagnosis rests on history and physical findings.³⁴ Whether inhalation injury carries the same independent risk where diagnostic and critical care resources are limited is therefore unclear. It is also unknown how much of the large crude difference in mortality reflects the larger, deeper burns and older age of affected patients.

The contribution of this study is threefold. First, it pools only multivariable-adjusted estimates of the association between inhalation injury and mortality. Second, it keeps adjusted odds ratios, hazard ratios and risk ratios separate. Third, it measures, within the same cohorts, how far adjustment attenuates the crude association. The review also asked whether the effect differs between high-income and low- and middle-income countries, between bronchoscopic and clinical diagnosis, and between models with and without post-injury mediators. The aim was to estimate the independent prognostic association between fire-related smoke inhalation injury and mortality in hospitalized burn patients and to assess the certainty of this evidence.

2. Methods

2.1. Study design

This systematic review and meta-analysis of prognostic factor studies was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.³⁵ The review question was framed by population, index prognostic factor, comparator, outcome, timing and setting. The population was patients hospitalized with burns; the prognostic factor smoke inhalation injury; the comparator patients without inhalation injury; and the outcome all-cause mortality after multivariable adjustment. Exposure was defined at admission, the outcome during the index admission or a fixed early follow-up, and the setting was hospital burn services in any country. The protocol was not registered. The eligibility criteria, data items and analysis plan were specified before screening. Ethical approval was not required because only published aggregate data were analyzed.

2.2. Search strategy

PubMed/MEDLINE, Europe PMC, OpenAlex and Scopus were searched from inception without language or date restrictions; the Scopus search was limited to journal articles.

Four concept blocks were combined: inhalation injury, burns, mortality or survival, and prognostic or multivariable analysis. The PubMed string was: ("Smoke Inhalation Injury"[Mesh] OR "Burns, Inhalation"[Mesh] OR "inhalation injur"[tiab] OR "inhalational injur"[tiab] OR "smoke inhalation"[tiab] OR "inhalation trauma"[tiab] OR "inhalation burn"[tiab] OR "airway burn"[tiab] OR "respiratory tract burn"[tiab]) AND ("Burns"[Mesh] OR burn[tiab] OR "thermal injur"[tiab]) AND ("Mortality"[Mesh] OR "Hospital Mortality"[Mesh] OR "Fatal Outcome"[Mesh] OR mortality[tiab] OR death[tiab] OR died[tiab] OR surviv[tiab] OR nonsurviv[tiab] OR fatal[tiab] OR lethal[tiab]) AND ("Logistic Models"[Mesh] OR "Proportional Hazards Models"[Mesh] OR "Multivariate Analysis"[Mesh] OR "Risk Factors"[Mesh] OR "Prognosis"[Mesh] OR multivariate[tiab] OR multivariable[tiab] OR "logistic regression"[tiab] OR Cox[tiab] OR regression[tiab] OR adjusted[tiab] OR predictor[tiab] OR "risk factor"[tiab] OR prognos[tiab] OR independent[tiab] OR "odds ratio"[tiab] OR "hazard ratio"[tiab]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh]). The strings for the other databases translated the same terms into each interface's syntax (title, abstract and keyword fields) and are reproduced in full in Supplementary Table S1.

The fourth concept block was broad. It included general terms such as predictor, risk factor, prognosis, independent and regression, so that studies reporting a model only in the full text would still be captured if the abstract described mortality predictors. To mitigate any residual loss, the reference lists of all included studies were searched, and every burn-mortality record they contained that had not been identified by the database searches was screened with the same criteria. Embase and Web of Science were not searched, which may have missed relevant cohorts (see Limitations).

2.3. Eligibility criteria

Studies were eligible when they were cohort, registry or database studies of hospitalized burn patients in which inhalation injury varied within the cohort, mortality was an outcome, and a multivariable-adjusted estimate for inhalation injury was reported. The estimate had to be accompanied by its confidence interval (CI) or by data from which the interval could be obtained exactly. Inhalation injury had to be the exposure of interest or a candidate predictor in a model of mortality predictors. Models in which it served only as an adjustment covariate for another exposure were excluded, because such coefficients are not designed to estimate the prognostic association and are reported inconsistently. Only peer-reviewed articles in journals indexed in MEDLINE, Scopus or Web of Science were eligible. The full criteria are detailed in Table 1.

Table 1. Eligibility criteria.

Element	Inclusion	Exclusion
Population	Patients of any age admitted to hospital with acute burn injury (burn unit or center, burn or general ICU, ward; registry and administrative cohorts included)	Prehospital or autopsy series of fire victims; isolated smoke inhalation or carbon monoxide poisoning without burns; non-burn populations
Prognostic factor	Smoke (fire-related) inhalation injury diagnosed clinically, bronchoscopically or from registry or administrative coding	Inhalation injury only within a composite score or exposure (for example revised Baux score, inhalation injury requiring mechanical ventilation); bronchoscopic grade comparisons within patients who all had inhalation injury
Comparator	Patients without inhalation injury in the same cohort	No within-cohort comparison
Outcome	All-cause mortality (in-hospital, intensive care, 28- or 30-day, or study-defined)	Mortality not analyzed; composite outcomes only
Effect measure	Multivariable-adjusted OR, HR or RR for inhalation injury with its 95% CI, or a logistic coefficient with its SE or CI	Univariate estimates only; estimate without CI or SE; internally impossible estimates (point estimate at or outside its CI, CI incompatible with the number of events)
Analysis	Inhalation injury was the exposure of interest or a candidate predictor in a model of mortality predictors	Inhalation injury entered only as an adjustment covariate in a model built for another exposure
Study design and report	Prospective or retrospective cohort, registry or database study, published as a peer-reviewed article in a journal indexed in MEDLINE, Scopus or Web of Science	Reviews, case reports, conference abstracts, theses; overlapping reports of the same database and period (larger or more complete report retained)

Notes: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; RR, risk ratio; SE, standard error. No restriction on language, country or publication date was applied.

2.4. Study selection and data extraction

Records were merged and de-duplicated on PubMed identifier, digital object identifier and normalized title. Before screening, a rule-based filter removed records that were unequivocally ineligible: conference abstracts; reviews, systematic reviews, case reports, letters, editorials, guidelines and preprints; animal or laboratory studies; records without burns; and records whose abstract contained no mortality term, no inhalation or smoke term, or no prognostic or multivariable term. Every removed record whose abstract contained inhalation, mortality and multivariable terms was nevertheless read individually, and eligible cohorts among them were assessed in full. All remaining titles and abstracts were screened against the eligibility criteria, with a decision and reason recorded for each record.

When a full text could not be obtained, the abstract was accepted only if it reported the adjusted estimate with its CI. One reviewer screened records, extracted data and assessed risk of bias with standardized written forms. A second reviewer verified every inclusion decision, every extracted estimate and every risk-of-bias judgment against the source document, and disagreements were resolved by discussion.

The extraction form recorded the country and World Bank income group, design, data source and period, setting, age group, sample size, prevalence of inhalation injury and its diagnostic criteria, mortality and its definition, and death counts by inhalation status. It also recorded the adjusted effect measure and its CI, the covariates, model type and variable-selection method, and the role of inhalation injury in the model. Every recorded estimate was checked against the corresponding table or sentence of the source report.

When a study reported more than one multivariable model, the fullest model that adjusted at least for age and burn size was used. This applied to five cohorts; for example, when one cohort of older adults reported models with full-thickness and with total burn size, the model with total burn size was used because it matched the adjustment of most other studies.³⁶ When two reports described the same database or center over overlapping periods, the larger or more complete report was retained.

2.5. Risk of bias assessment

Risk of bias was assessed with the six domains of the Quality In Prognosis Studies (QUIPS) tool: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Confounding was rated low when both age and burn size were adjusted for, moderate when only one was, and high when neither was. The analysis domain considered the number of events per candidate variable, data-driven variable selection, the inclusion of post-injury mediators and the completeness of model reporting. Because QUIPS does not prescribe an overall judgment, a rule was specified in advance: overall risk was high when any domain was high, low when all domains were low or only one was moderate, and moderate otherwise. This mirrors the logic of domain-based risk-of-bias tools, in which a single serious concern determines the overall rating.

2.6. Statistical analysis

The primary effect measure was the adjusted odds ratio (OR) of death for patients with versus without inhalation injury. For each study the log OR and its standard error (SE) were obtained from the reported estimate and 95% CI (Equation 1).

$$y_i = \ln(OR_i), SE_i = \frac{\ln(UL_i) - \ln(LL_i)}{2 \times 1.96} \quad (1)$$

The SE was derived from the full width of the interval on the log scale. Intervals whose asymmetry indicated a misprint

(point estimate at or beyond a limit, or an interval incompatible with the number of events) were not used (Table 1). When only a logistic regression coefficient was printed, the OR and its interval were obtained by exponentiation (Equation 2). When death counts by inhalation status were available, the crude OR and its SE were computed from the 2×2 table (Equation 3).

$$OR_i = e^{\beta_i}, 95\% CI = e^{\beta_i \pm 1.96 \times SE(\beta_i)} \quad (2)$$

$$OR_i^{crude} = \frac{a_i d_i}{b_i c_i}, SE_i = \sqrt{\frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i}} \quad (3)$$

Log ORs were pooled with a random-effects model, because the adjusted estimates came from models with different covariates and populations and were not expected to share a single true value. The between-study variance was estimated with the DerSimonian-Laird method (Equation 4). Studies were weighted by the inverse of the sum of their within-study variance and the between-study variance (Equation 5).

$$\tau^2 = \max \left\{ 0, \frac{Q - (k-1)}{\sum_i w_i - \frac{\sum_i w_i^2}{\sum_i w_i}} \right\}, w_i = \frac{1}{SE_i^2} \quad (4)$$

$$\hat{\mu} = \frac{\sum_i w_i^* y_i}{\sum_i w_i^*}, w_i^* = \frac{1}{SE_i^2 + \tau^2} \quad (5)$$

CI for the pooled estimate used the Hartung-Knapp adjustment with a *t* distribution, in which *q* denotes the weighted residual variance (Equation 6). This combination was chosen as the primary analysis because it is robust when between-study variance is moderate to large; the restricted maximum likelihood and Paule-Mandel estimators were pre-specified sensitivity analyses.

$$\hat{\mu} \pm t_{k-1, 0.975} \sqrt{\frac{\sum_i w_i^* (y_i - \hat{\mu})^2}{(k-1) \sum_i w_i^*}} \quad (6)$$

Heterogeneity was quantified with Cochran's *Q*, τ^2 and I^2 (Equation 7). The 95% prediction interval, which uses *k* - 2 degrees of freedom (*k*, number of cohorts) and the SE of the pooled estimate, described the range of effects expected in a new cohort (Equation 8).

$$Q = \sum_i w_i (y_i - \hat{\mu}_{FE})^2, I^2 = \max \left\{ 0, \frac{Q - (k-1)}{Q} \right\} \times 100\% \quad (7)$$

$$\hat{\mu} \pm t_{k-2, 0.975} \sqrt{\tau^2 + SE^2(\hat{\mu})} \quad (8)$$

Adjusted hazard ratios (HRs) and risk ratios (RRs) were not combined with ORs in the primary analysis, because mortality was common in many cohorts and the measures then diverge. HRs were pooled separately, and a combined analysis of adjusted ORs and HRs was run as a sensitivity analysis. The two adjusted RRs were reported individually and not pooled. Ten subgroup variables were pre-specified: country income level, age group, care setting, bronchoscopic confirmation of inhalation injury, post-injury mediators in the model (mechanical ventilation, pneumonia, sepsis, organ failure or complications), world region, study size, overall risk of bias, data source and cohort era. Separate random-effects estimates were obtained within subgroups and compared with a test for subgroup differences. Random-effects meta-regression (restricted maximum likelihood with the Knapp-Hartung adjustment) examined five moderators: cohort mortality, prevalence of inhalation injury, mean or median burn size, publication year and the logarithm of sample size. No correction was made for multiple testing, so subgroup and meta-regression findings were interpreted as exploratory.

Subgroup variables were coded from the extraction form before analysis. Income group followed the World Bank classification for the country and period of data collection. Care setting was coded as intensive care or major burns when the cohort was restricted to intensive care admissions or to patients above a burn-size threshold, as emergency or prehospital when patients were enrolled at transport or emergency department arrival, and otherwise as all burn

admissions. Age group was coded as children, adults or older adults when the cohort was restricted accordingly, and otherwise as mixed. Diagnosis was coded as bronchoscopic when bronchoscopy confirmed inhalation injury in all or some patients. Cohort era used the mid-point of the period of data collection.

Sensitivity analyses used the restricted maximum likelihood and Paule-Mandel estimators, Wald-type intervals and a common-effect model. Further analyses excluded, in turn, studies at high risk of bias, studies assessed from abstracts, models without adjustment for both age and burn size, and models with post-injury mediators. Others excluded registry and database analyses, emergency or prehospital cohorts, models that also contained a composite score including inhalation injury, and estimates converted from coefficients. Leave-one-out analysis and influence diagnostics (studentized residuals and Cook's distances) were also performed.

Small-study effects were examined with a funnel plot, the Egger regression test (Equation 9), the Begg rank correlation test and the trim-and-fill method, as more than ten studies were available.

$$\frac{y_i}{SE_i} = \beta_0 + \beta_1 \frac{1}{SE_i} + \varepsilon_i \quad (9)$$

In cohorts that reported both an adjusted OR and death counts by inhalation status, crude and adjusted ORs were pooled in parallel. The within-study ratio of the adjusted to the crude OR summarized the attenuation produced by adjustment (Equation 10).

$$ROR_i = \frac{OR_i^{\text{adjusted}}}{OR_i^{\text{crude}}}, \text{attenuation} = (1 - ROR_i) \times 100\% \quad (10)$$

Certainty of evidence was rated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for prognostic factor research, starting at high certainty for cohort studies. Inconsistency was judged

mainly from the prediction interval, because I^2 increases with study size and does not indicate whether estimates disagree in direction. Publication bias was judged from the funnel plot, the Egger test and the potential for selective reporting of predictors. Analyses were performed in R 4.5.3 with the meta package (8.2.1; functions metagen, metabin, metainf, metabias and trimfill) and the metafor package (4.8.0; functions rma and influence). Two-sided $p < 0.05$ indicated statistical significance.

3. Results

3.1. Study selection

The database searches identified 3,645 records (PubMed 931, Europe PMC 710, OpenAlex 1,177, Scopus 827). After removal of 2,128 duplicates and 487 records excluded by the rule-based filter, 1,030 records were screened. In all, 340 reports were sought in full; 122 could not be obtained and 218 were assessed for eligibility. Of these, 165 were excluded. The most common reason was the absence of a usable adjusted estimate for inhalation injury (113 reports): 48 reported only univariate or descriptive comparisons; in 20, inhalation injury entered a multivariable model but was not retained or was not reported; 14 gave an estimate without a CI; 13 used other effect measures; 6 reported grade-specific estimates only; and 12 reported implausible or internally inconsistent estimates. A further 26 reports used inhalation injury only as a covariate for another exposure. The remaining 26 exclusions were conference abstracts, theses or reports in non-indexed journals (8), overlapping populations (8), absence of a with-versus-without comparison (5), composite exposures (3) and mortality not analyzed (2). Citation searching added 170 records but no further eligible study. In total, 53 cohorts were included: 44 reported adjusted ORs, 7 adjusted HRs and 2 adjusted RRs. The selection process is illustrated in Figure 1.

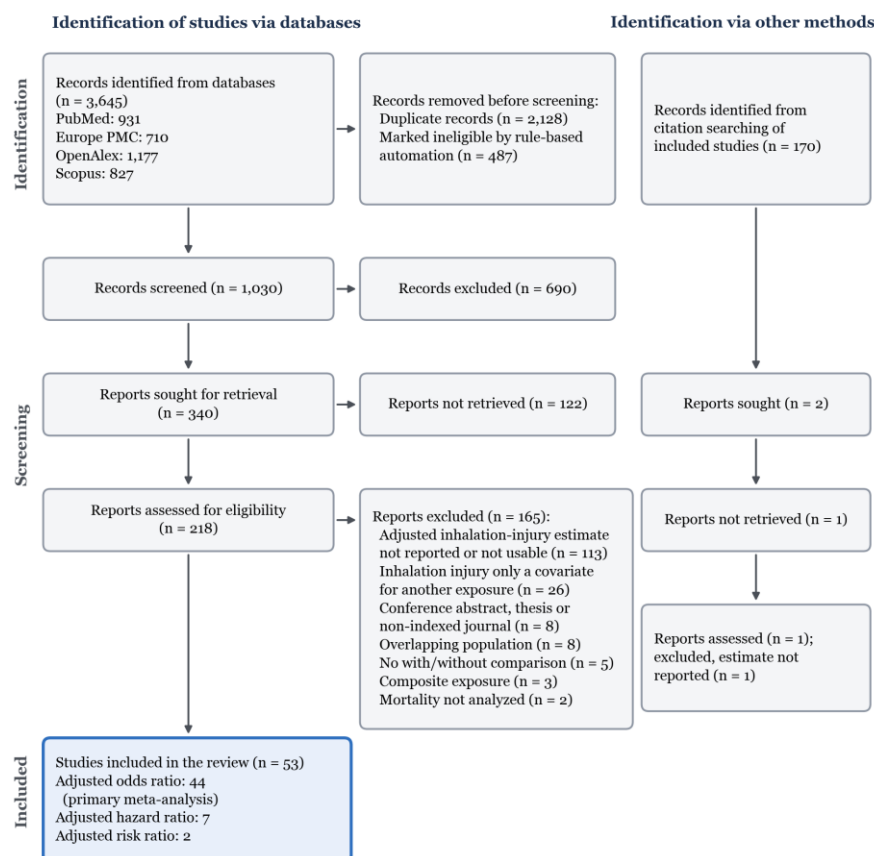


Figure 1. PRISMA 2020 flow diagram of the identification, screening and inclusion of cohort studies reporting adjusted estimates for inhalation injury and mortality. HR, hazard ratio; OR, odds ratio; RR, risk ratio.

3.2. Characteristics of the included studies

The 53 cohorts included 338,479 patients from 28 countries; their characteristics are detailed in Table 2. Twenty-eight cohorts came from low- and middle-income countries and 25 from high-income countries, distributed across Asia-Pacific (24), Europe (11), North America (9) and Africa, the Middle East and Latin America (9). Single-center cohorts numbered 41, most of them retrospective; 6 were multicenter and 6 used national registries or administrative databases. The largest included 137,061, 73,774 and 66,611 patients.^{37–39}

Twenty-five cohorts were restricted to intensive care or major burns, 26 included all burn admissions and 2 enrolled patients transported by emergency medical services. By age, 24 cohorts enrolled adults, 4 children, 5 older adults and 20 mixed ages. The median prevalence of inhalation injury was 24.2% (range 0.3–73.3%), based on the 47 cohorts with a reported percentage or count. The median mortality was 16.9% (range 0.6–64.5%); it was 17.0% in high-income and

16.4% in low- and middle-income cohorts, many of them intensive care cohorts. Bronchoscopy contributed to the diagnosis in 18 cohorts, clinical criteria alone were used in 8, registry or administrative codes in 3, and the diagnostic criteria were not reported in 24. Models adjusted for both age and burn size in 41 cohorts, and 19 models (17 of the 44 in the primary analysis) also contained post-injury mediators. In the primary analysis, 9 estimates came from abstracts and 4 were converted from logistic coefficients.

Beyond age and burn size, the final models most often included sex (20 cohorts), burn depth or full-thickness area (19), comorbidity (12) and burn mechanism (9); 6 models also contained a composite severity score, and 5 included ventilation-related variables. Variable selection was data-driven (univariable screening, stepwise or backward elimination) in most single-center cohorts, whereas registry analyses usually fitted pre-specified models.

Table 2. Characteristics of the included cohorts.

Study	Country (income group)	Data source; period	Age group; setting	n total; n with inhalation injury (%)	Mortality (%)	Diagnosis	Adjusted estimate (95% CI)	Adjusted for age/burn size/mediators	QUIPS
Adjusted odds ratio (primary meta-analysis)									
Suzuki 2005 ⁴⁰	Japan (HIC)	multicenter; 1984–2002	Mixed ages; ICU or major burns	5,560; 1,690 (30.4%)	15.8	Bronchoscopy	2.58 (2.03–3.29)	Yes/Yes/No	Moderate
Steinsträsser 2007 ⁴¹	Germany (HIC)	single center; 1995–2004	Adults; ICU or major burns	96; NR	NR	Non-bronchoscopic or NR	5.95 (1.72–20.55)	Yes/No/Yes	High
Othman 2011 ⁴²	Iraq (LMIC)	single center; 2006	Mixed ages; all burn admissions	947; NR	28.0	Non-bronchoscopic or NR	9.80 (4.80–20.00)	Yes/Yes/No	Moderate
Stylianou 2014 ³⁹	England and Wales (UK) (HIC)	registry or database; 2003–2011	Mixed ages; all burn admissions	66,611; 776 (1.2%)	1.3	Non-bronchoscopic or NR	6.39 (4.87–8.38) ^a	Yes/Yes/No	Moderate
Seo 2015 ⁴³	South Korea (HIC)	single center; 2003–2012	Mixed ages; ICU or major burns	4,481; 1,291 (28.8%)	23.8	Bronchoscopy	2.52 (2.05–3.09)	Yes/Yes/No	Moderate
Dhopte 2017 ⁴⁴	India (LMIC)	single center; 2014	Children; all burn admissions	475; 74 (15.6%)	31.3	Non-bronchoscopic or NR	1.94 (0.66–5.66)	Yes/Yes/Yes	Moderate
Monteiro 2017 ⁴⁵	Portugal (HIC)	single center; NR	Adults; all burn admissions	210; 82 (39.0%)	18.6	Bronchoscopy	1.04 (0.20–5.44)	Yes/Yes/Yes	High
Shahabi 2017 ⁴⁶	Iran (LMIC)	single center; 2011	Mixed ages; all burn admissions	1,200; NR (20.8%)	15.5	Non-bronchoscopic or NR	2.11 (1.28–2.88)	Yes/Yes/No	High
Capek 2018 ⁴⁷	United States (HIC)	single center; 1989–2017	Mixed ages; all burn admissions	10,384; NR (12.2%)	3.4	Bronchoscopy	3.35 (2.30–4.89) ^a	Yes/Yes/No	Low
Chong 2018 ⁴⁸	Singapore (HIC)	single center; 2015–2016	Adults; all burn admissions	202; 35 (17.3%)	3.5	Bronchoscopy	0.60 (0.01–44.53)	Yes/Yes/No	High
Yen 2018 ³⁸	Taiwan (HIC)	registry or database; 2003–2013	Mixed ages; all burn admissions	73,774; NR	NR	Non-bronchoscopic or NR	2.71 (2.05–3.60)	Yes/Yes/No	Moderate
Zavlin 2018 ³⁷	United States (HIC)	registry or database; 2002–2011	Mixed ages; all burn admissions	137,061; 7,468 (5.4%)	3.3	Non-bronchoscopic or NR	3.84 (3.38–4.36)	Yes/Yes/Yes	Moderate
Boissin 2019 ⁴⁹	South Africa (LMIC)	single center; 2015–2016	Adults; all burn admissions	263; 164 (62.4%)	27.7	Non-bronchoscopic or NR	1.20 (0.47–3.06)	No/Yes/No	Moderate
Cheng 2019 ⁵⁰	China (LMIC)	multicenter; 2014	Mixed ages; ICU or major burns	2,483; 804 (32.4%)	9.8	Non-bronchoscopic or NR	6.65 (4.52–9.79)	Yes/Yes/No	Moderate
Güldoğan 2019 ⁵¹	Turkey (LMIC)	single center; 2008	Mixed ages; ICU or major burns	224; 98 (43.8%)	44.2	Non-bronchoscopic or NR	1.37 (1.03–1.82)	Yes/Yes/Yes	Moderate
Lam 2019 ⁵²	Vietnam (LMIC)	single center; 2016–2018	Older adults; all burn admissions	416; 14 (3.4%)	9.9	Non-bronchoscopic or NR	65.37 (5.99–706.27) ^a	Yes/Yes/No	High
Lip 2019 ⁵³	Malaysia (LMIC)	single center; 2010–2017	Adults; ICU or major burns	525; 154 (29.3%)	11.8	Non-bronchoscopic or NR	0.99 (0.32–3.05)	Yes/Yes/Yes	Moderate
Liu 2019 ⁵⁴	United States (HIC)	single center; NR	Adults; ICU or major burns	318; NR	17.0	Non-bronchoscopic or NR	2.69 (1.04–6.93)	Yes/Yes/No	High
Newberry 2019 ⁵⁵	India (LMIC)	multicenter; 2015	Mixed ages; emergency or prehospital cohort	439; NR	64.5	Non-bronchoscopic or NR	5.50 (2.50–12.20)	Yes/Yes/No	High
Christofides 2020 ⁵⁶	South Africa (LMIC)	single center; 2005–2015	Adults; all burn admissions	2,055; 410 (20.0%)	21.1	Non-bronchoscopic or NR	3.52 (2.25–4.90)	Yes/Yes/No	Moderate
Lam 2021 ⁵⁷	Vietnam (LMIC)	single center; 2015–2019	Children; all burn admissions	7,713; 24 (0.3%)	0.6	Non-bronchoscopic or NR	8.67 (2.12–35.52) ^a	Yes/Yes/No	High
McCorry 2021 ⁵⁸	United States (HIC)	registry or database; 2009–2017	Children; ICU or major burns	2,056; NR (5.1%)	4.5	Non-bronchoscopic or NR	5.39 (1.58–18.42)	NR/Yes/Yes	Moderate
Qiu 2021 ⁵⁹	China (LMIC)	multicenter; 2008–2015	Adults; ICU or major burns	577; 165 (28.6%)	9.5	Non-bronchoscopic or NR	2.06 (0.99–4.27)	Yes/Yes/Yes	High
Keyloun 2022 ⁹	United States (HIC)	single center; 2012–2017	Adults; all burn admissions	112; 28 (25.0%)	17.0	Bronchoscopy	0.53 (0.08–3.46)	Yes/Yes/No	High

Study	Country (income group)	Data source; period	Age group; setting	<i>n</i> total; <i>n</i> with inhalation injury (%)	Mortality (%)	Diagnosis	Adjusted estimate (95% CI)	Adjusted for age/burn size/mediators	QUIPS
Adjusted odds ratio (primary meta-analysis)									
Wardhana 2022 ⁶⁰	Indonesia (LMIC)	single center; 2016–2020	Adults; all burn admissions	220; 29 (13.2%)	25.9	Bronchoscopy	2.77 (1.04–5.43)	No/Yes/No	Moderate
Xu 2022 ⁶¹	China (LMIC)	single center; 2008–2018	Adults; ICU or major burns	244; 168 (68.9%)	16.0	Non-bronchoscopic or NR	1.84 (0.50–6.81)	Yes/Yes/No	High
Bagheri 2023 ⁶²	Germany (HIC)	registry or database; 2016–2019	Adults; ICU or major burns	7,276; 984 (13.5%)	8.8	Non-bronchoscopic or NR	2.79 (2.17–3.60)	Yes/Yes/No	Moderate
Chen 2023 ⁶³	China (LMIC)	single center; 2018–2022	Adults; ICU or major burns	361; 103 (28.5%)	5.8	Non-bronchoscopic or NR	3.14 (1.15–8.56)	Yes/Yes/Yes	High
Li 2023 ⁶⁴	China (LMIC)	single center; 2017–2022	Adults; ICU or major burns	88; 56 (63.6%)	28.4	Non-bronchoscopic or NR	5.98 (1.42–15.39)	No/No/Yes	High
Martens 2023 ⁶⁵	United States (HIC)	single center; 2009–2020	Children; ICU or major burns	69; NR (40.0%)	25.0	Non-bronchoscopic or NR	3.40 (1.05–11.00)	NR/NR/NR	High
Pan 2023 ⁶⁶	China (LMIC)	single center; 2017–2021	Adults; ICU or major burns	135; 99 (73.3%)	27.4	Non-bronchoscopic or NR	2.84 (0.67–11.54)	No/Yes/Yes	High
Josuttis 2024 ⁶⁷	Germany (HIC)	single center; 2014–2019	Adults; ICU or major burns	90; 46 (51.1%)	34.4	Bronchoscopy	3.57 (1.36–9.36)	Yes/Yes/Yes	High
Bulut 2025 ⁶⁸	Turkey (LMIC)	single center; 2019–2023	Mixed ages; emergency or prehospital cohort	784; 48 (6.1%)	5.0	Non-bronchoscopic or NR	3.33 (1.22–9.07)	Yes/Yes/No	High
Dincer 2025 ⁶⁹	Turkey (LMIC)	single center; 2007–2024	Adults; ICU or major burns	100; 27 (27.0%)	23.0	Non-bronchoscopic or NR	10.93 (2.43–49.11)	No/No/No	High
Neo 2025 ⁷⁰	Singapore (HIC)	single center; 2019–2023	Adults; all burn admissions	649; 227 (35.0%)	3.4	Bronchoscopy	1.60 (0.44–9.48)	Yes/Yes/No	High
Zeaiter 2025 ⁷¹	Lebanon (LMIC)	single center; 2017–2023	Mixed ages; all burn admissions	474; 150 (31.6%)	16.7	Non-bronchoscopic or NR	0.98 (0.35–2.75)	Yes/Yes/Yes	High
Alshdowh 2026 ⁷²	Jordan (LMIC)	single center; 2018–2022	Mixed ages; all burn admissions	493; 127 (25.8%)	15.6	Bronchoscopy	3.64 (1.49–8.88)	Yes/Yes/No	Moderate
Bayou 2026 ⁷³	Ethiopia (LMIC)	multicenter; 2021–2023	Mixed ages; all burn admissions	800; 112 (14.0%)	8.5	Non-bronchoscopic or NR	6.53 (2.14–19.95)	No/Yes/Yes	High
Cueva-Ramírez 2026 ⁷⁴	Dominican Republic (LMIC)	single center; 2020–2024	Adults; all burn admissions	1,005; 180 (17.9%)	32.2	Bronchoscopy	2.09 (0.98–4.46)	Yes/Yes/Yes	Moderate
Dung 2026 ⁷⁵	Vietnam (LMIC)	single center; 2023	Adults; all burn admissions	395; 85 (21.5%)	12.2	Non-bronchoscopic or NR	7.30 (5.20–17.00)	No/Yes/Yes	High
Goder 2026 ³⁶	Canada (HIC)	single center; 2018–2023	Older adults; all burn admissions	109; 24 (22.0%)	45.9	Non-bronchoscopic or NR	4.04 (0.92–21.80)	Yes/Yes/No	Moderate
Lam 2026 ⁷⁶	Vietnam (LMIC)	single center; 2021–2025	Older adults; ICU or major burns	604; 21 (3.5%)	7.6	Non-bronchoscopic or NR	6.96 (1.44–33.64)	Yes/Yes/No	Moderate
Schmitt 2026 ⁷⁷	France (HIC)	single center; 2012–2025	Older adults; ICU or major burns	243; 51 (21.0%)	35.0	Bronchoscopy	2.81 (1.12–7.05)	Yes/Yes/No	Moderate
Tomaka 2026 ⁷⁸	Poland (HIC)	single center; 2018–2022	Adults; ICU or major burns	144; 59 (41.0%)	43.1	Bronchoscopy	3.76 (1.46–9.66)	Yes/Yes/Yes	Moderate
Adjusted hazard ratio									
Mahar 2008 ⁷⁹	Australia (HIC)	single center; 2002–2006	Older adults; all burn admissions	80; 12 (15.0%)	18.8	Bronchoscopy	17.70 (3.07–101.00)	Yes/Yes/No	High
Wu 2018 ⁸⁰	China (LMIC)	single center; 2010–2015	Mixed ages; ICU or major burns	142; NR	NR	Non-bronchoscopic or NR	4.08 (1.14–14.56)	NR/Yes/No	High
Toppi 2019 ⁸¹	Australia and New Zealand (HIC)	registry or database; 2009–2013	Adults; ICU or major burns	496; 200 (40.3%)	16.9	Non-bronchoscopic or NR	2.14 (1.21–3.78)	Yes/Yes/No	Moderate
Panwar 2020 ⁸²	India (LMIC)	single center; 2018	Mixed ages; all burn admissions	100; 7 (7.0%)	NR	Non-bronchoscopic or NR	3.95 (1.00–15.57)	Yes/Yes/Yes	High
Seo 2022 ⁸³	South Korea (HIC)	single center; 2013–2020	Adults; ICU or major burns	934; 341 (36.5%)	22.5	Bronchoscopy	1.64 (1.22–2.20)	Yes/Yes/Yes	Moderate
Abarca 2023 ⁸⁴	Spain (HIC)	single center; 2011–2018	Mixed ages; all burn admissions	2,651; 143 (5.4%)	3.5	Bronchoscopy	3.30 (2.15–5.07)	Yes/Yes/No	Moderate
Karikari 2025 ⁸⁵	Ghana (LMIC)	single center; 2021–2023	Mixed ages; all burn admissions	457; 53 (11.6%)	21.2	Non-bronchoscopic or NR	1.66 (1.05–2.61)	No/Yes/No	Moderate
Adjusted risk ratio									
Sood 2016 ⁸⁶	United States (HIC)	multicenter; 2003–2010	Adults; ICU or major burns	324; 127 (39.2%)	20.0	Bronchoscopy	2.08 (1.35–3.21)	Yes/Yes/No	Moderate
Witt 2021 ⁸⁷	United States (HIC)	single center; 2009–2015	Mixed ages; ICU or major burns	830; 201 (24.2%)	12.2	Bronchoscopy	2.35 (1.66–3.31)	Yes/Yes/No	Low

Notes: Estimates are shown as reported (adjusted for the covariates of each study’s multivariable model). Adjustment column: age / burn size (total body surface area or a score containing it) / post-injury mediators (for example mechanical ventilation, pneumonia, sepsis, organ failure or complications). ^a Odds ratio and 95% CI obtained by exponentiating the reported logistic coefficient and its CI (or coefficient $\pm$ 1.96 standard errors). HIC, high-income country; ICU, intensive care unit; LMIC, low- or middle-income country (World Bank classification at the time of the study); NR, not reported; QUIPS, Quality In Prognosis Studies risk of bias.

3.3. Risk of bias

Overall risk of bias was low in 2 cohorts, moderate in 26 and high in 25, as shown in Figure 2. Outcome measurement was at low risk in almost all studies because mortality was recorded objectively. Statistical analysis and reporting was the domain most often at high risk. This reflected few events

per variable, stepwise selection and adjustment for post-injury complications. Prognostic factor measurement was the next most frequent concern, because diagnostic criteria were undefined or registry-coded in many cohorts. Across domains, high risk was judged in 20 cohorts for statistical analysis and reporting, 13 for prognostic factor

measurement, 4 for attrition and 3 each for participation and confounding, whereas no cohort was at high risk for outcome measurement.

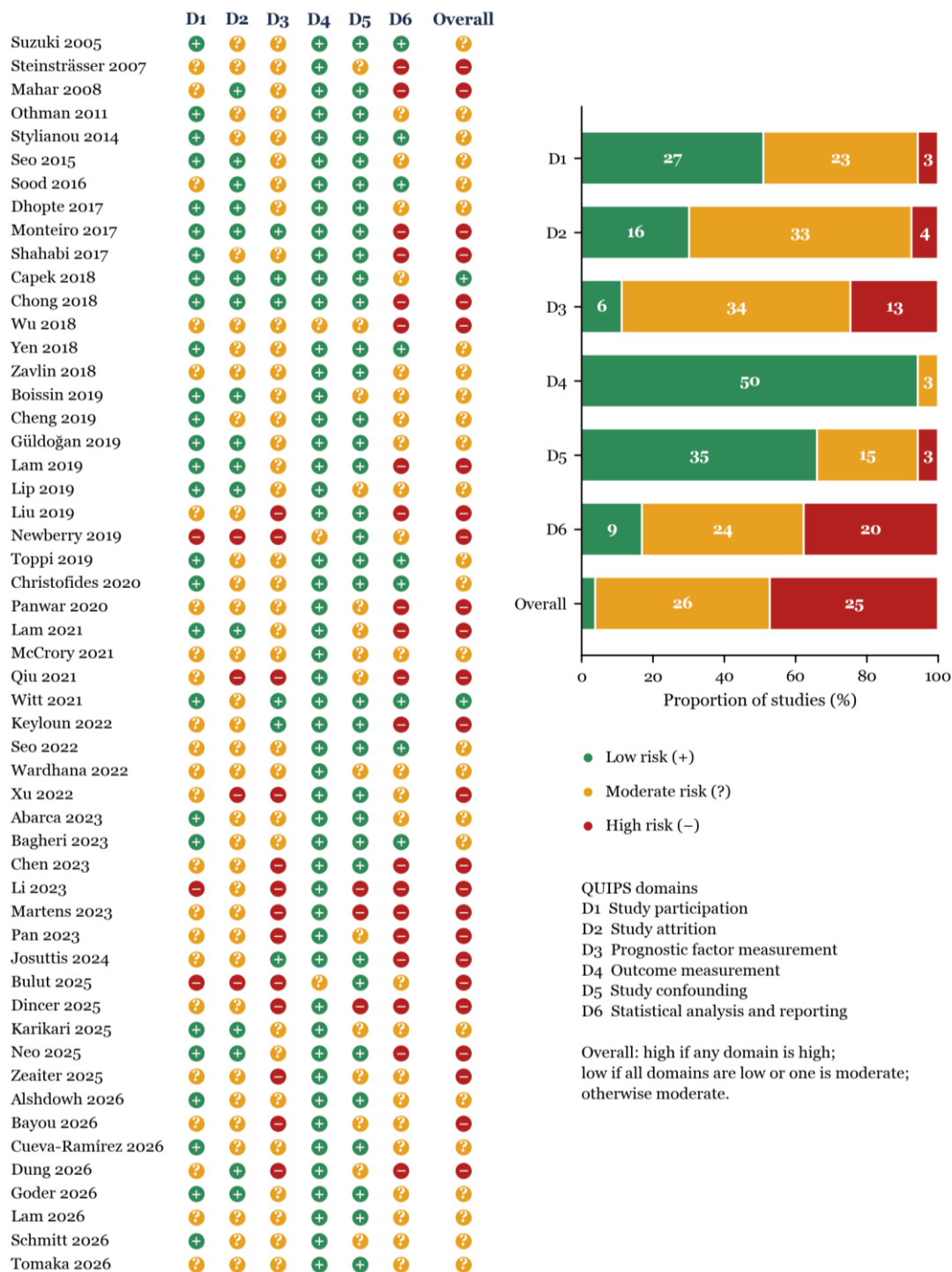


Figure 2. Risk of bias of the included cohorts assessed with the Quality In Prognosis Studies (QUIPS) tool. Left, judgment for each study and domain (+, low; ?, moderate; -, high); right, proportion of studies at each level of risk per domain, with the counts of studies shown in the bars. D1, study participation; D2, study attrition; D3, prognostic factor measurement; D4, outcome measurement; D5, study confounding; D6, statistical analysis and reporting.

3.4. Adjusted association between inhalation injury and mortality

Across 44 cohorts with 332,465 patients, inhalation injury was associated with higher adjusted odds of death (pooled OR 3.23, 95% CI 2.67–3.90; $p < 0.001$; see Figure 3). Study estimates ranged from 0.53 to 65.37. The lower confidence limit exceeded 1 in 31 cohorts, and the point estimate was below 1 in 4, all with wide intervals.^{9,48,53,71} Heterogeneity

was substantial (Q 155.4, df 43, $p < 0.001$; I^2 72.3%, 95% CI 62.7–79.5%; τ^2 0.156), but the 95% prediction interval (1.43–7.30) did not include 1. The main pooled estimates are detailed in Table 3. The largest registry and database cohorts gave estimates between 2.71 and 6.39: 3.84 in the United States National Burn Repository, 2.71 in the Taiwanese National Health Insurance database, 6.39 in the England and Wales burn database and 2.79 in the German Burn Registry.^{37–39,62}

k = 44 | Random effects (DerSimonian–Laird, Hartung–Knapp) | $I^2 = 72.3\%$ | $\tau^2 = 0.156$

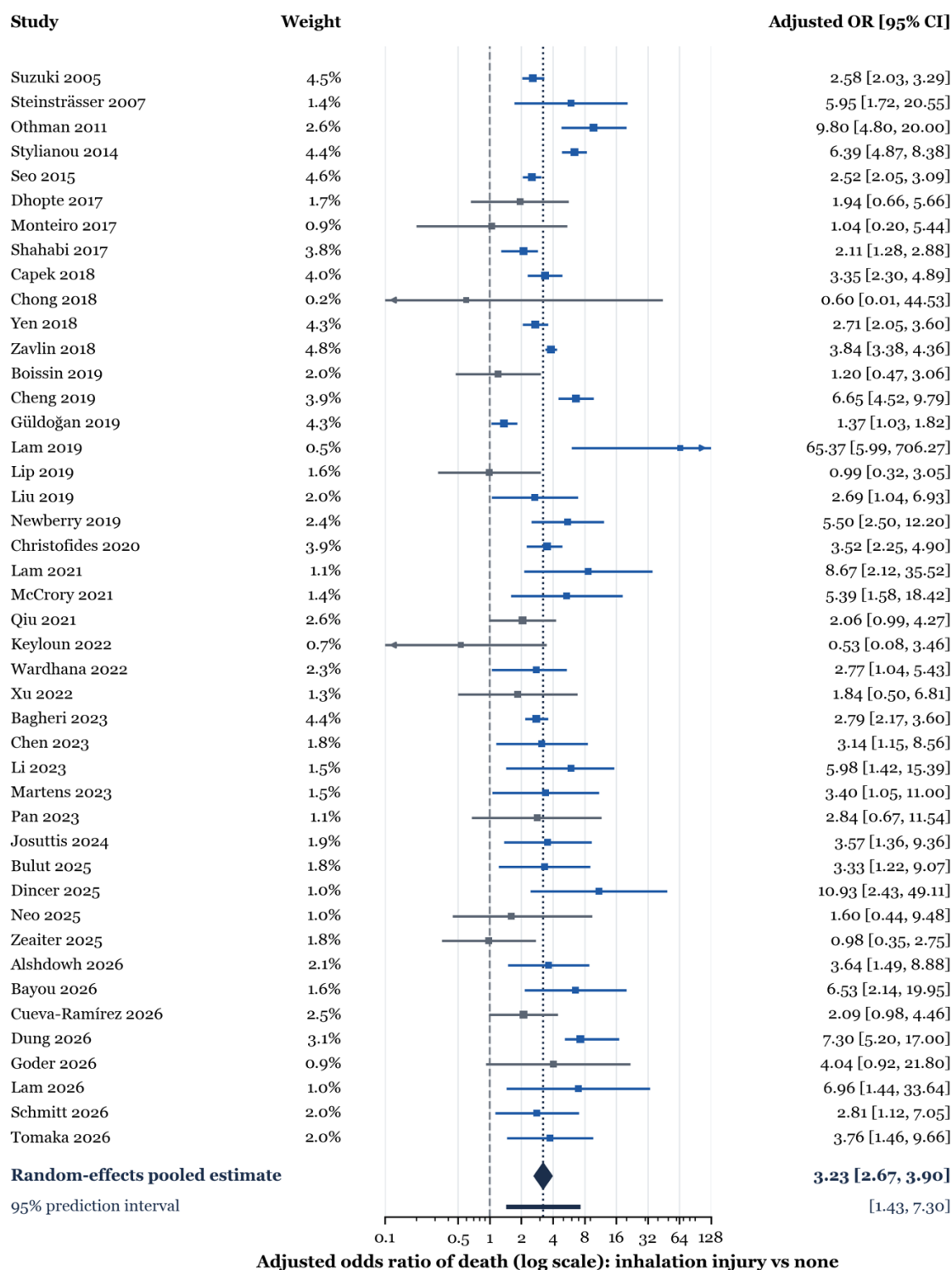


Figure 3. Forest plot of multivariable-adjusted odds ratios of death for patients with versus without inhalation injury. Squares are study estimates (size proportional to random-effects weight) with their reported 95% confidence intervals; blue indicates an interval entirely above 1. The diamond is the random-effects pooled estimate (DerSimonian–Laird, Hartung–Knapp) and the bar beneath it the 95% prediction interval. The dashed vertical line marks OR = 1 and the dotted vertical line the pooled estimate. Weights were derived from the standard error implied by each reported interval on the log scale.

Adjusted HRs came from 7 cohorts that used Cox models, 4 of them in all burn admissions and 3 in intensive care or major burns, from Australia and New Zealand, China, India, South Korea, Spain and Ghana.^{79–85} Their pooled HR was 2.46 (1.45–4.19) ($p = 0.006$; $I^2 = 61.6\%$) (Supplementary Figure S1). The two cohorts that used Poisson models reported adjusted RRs (Sood 2016: 2.08, 95% CI 1.35–3.21;⁸⁶ Witt 2021: 2.35, 1.66–

3.31).⁸⁷ Adjusted estimates for respiratory complications were reported by only two cohorts and were not pooled. In a United States cohort, inhalation injury was associated with pneumonia (adjusted RR 1.76, 95% CI 1.17–2.65) but not significantly with ARDS (1.18, 0.94–1.48).⁸⁷ In a Singapore cohort, ARDS developed in 48.6% of patients with inhalation injury and 0.6% of those without.⁴⁸

Table 3. Pooled estimates and sensitivity analyses.

Analysis	k	Estimate (95% CI)	I ² (%)	95% PI
Main analyses				
Adjusted OR, random effects (primary)	44	3.23 (2.67–3.90)	72.3	1.43–7.30
Adjusted HR	7	2.46 (1.45–4.19)	61.6	–
Crude OR from 2×2 counts	27	9.45 (6.40–13.95)	89.2	2.54–35.11
Paired cohorts: crude OR	23	9.61 (6.22–14.86)	–	–
Paired cohorts: adjusted OR	23	2.92 (2.17–3.94)	–	–
Sensitivity analyses of the adjusted OR				
REML + Hartung–Knapp	44	3.23 (2.67–3.91)	72.3	–
Paule–Mandel + Hartung–Knapp	44	3.23 (2.66–3.92)	72.3	–
DL, Wald-type CI (no HK)	44	3.23 (2.72–3.83)	72.3	–
Common-effect (inverse variance)	44	3.23 (3.02–3.46)	–	–
Low or moderate overall risk of bias only	22	3.16 (2.50–4.00)	81.6	–
Full-text-assessed studies only	35	3.02 (2.43–3.75)	73.0	–
Adjusted for both age and burn size	34	3.04 (2.46–3.75)	75.9	–
Models without post-injury mediators	27	3.46 (2.73–4.38)	70.0	–
Excluding national registry/database analyses	39	3.11 (2.50–3.88)	66.0	–
Excluding the influential study (Güldoğan 2019)	43	3.36 (2.81–4.03)	64.4	–
Excluding emergency or prehospital cohorts	42	3.18 (2.62–3.87)	73.3	–
Excluding models containing a composite score with inhalation injury	43	3.25 (2.67–3.96)	72.7	–
Estimates reported directly as OR (no coefficient conversion)	40	3.03 (2.52–3.64)	67.7	–
Adjusted ORs and HRs combined	51	3.11 (2.61–3.70)	73.4	–

Notes: Random-effects models used the DerSimonian–Laird estimator of τ^2 with the Hartung–Knapp adjustment unless stated otherwise. Paired cohorts: studies reporting both an adjusted OR and death counts by inhalation status; median ratio of adjusted to crude OR 0.30 (interquartile range 0.18–0.58). CI, confidence interval; DL, DerSimonian–Laird; HK, Hartung–Knapp; HR, hazard ratio; k, number of cohorts; OR, odds ratio; PI, prediction interval; REML, restricted maximum likelihood.

3.5. Crude versus adjusted estimates

Death counts by inhalation status were available for 27 cohorts (35,566 patients). Mortality was 37.5% with inhalation injury and 5.7% without it, and the pooled crude OR was 9.45 (6.40–13.95) (I^2 89.2%). In the 23 cohorts that reported both measures, the pooled OR fell from 9.61 (6.22–14.86) before adjustment to 2.92 (2.17–3.94) after

adjustment, as illustrated in Figure 4. The adjusted OR was smaller than the crude OR in 21 of 23 cohorts. The median ratio of adjusted to crude OR was 0.30 (interquartile range 0.18–0.58), corresponding to an attenuation of about 70%. The paired cohorts were smaller than the other cohorts in the primary analysis (median 416 versus 649 patients) but similar in setting (10 and 10 intensive care cohorts, respectively).

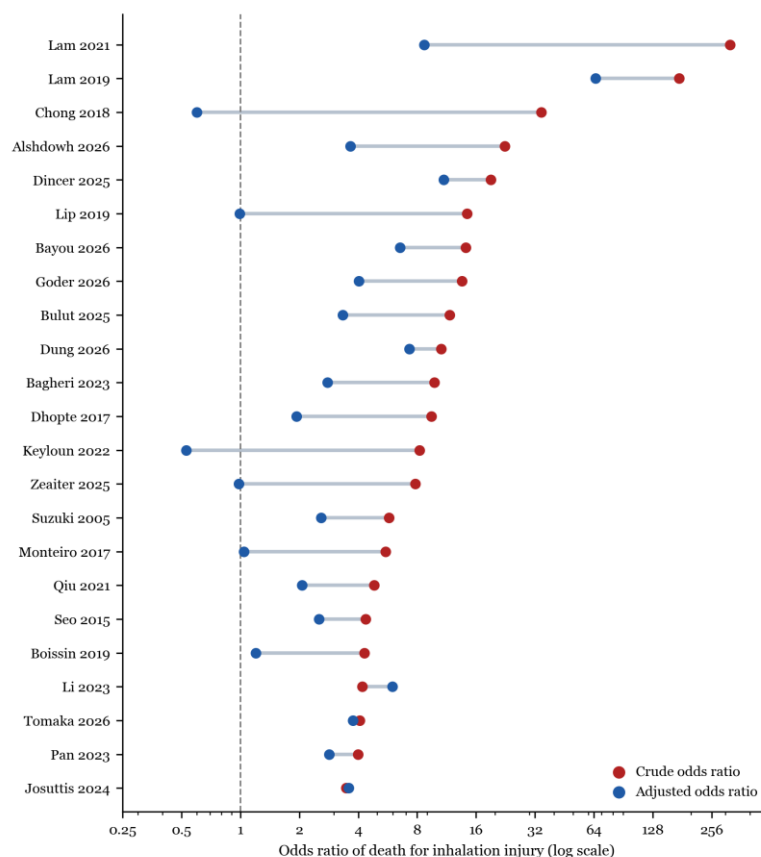


Figure 4. Crude (red) and multivariable-adjusted (blue) odds ratios of death for inhalation injury in the 23 cohorts that reported both, ordered by the crude estimate. Crude estimates are red circles and adjusted estimates blue circles, joined by a line. Pooled crude OR 9.61 (6.22–14.86); pooled adjusted OR 2.92 (2.17–3.94); median ratio of adjusted to crude OR 0.30. CI, confidence interval; OR, odds ratio.

3.6. Subgroup analyses and meta-regression

The adjusted association was similar in high-income (3.20, 95% CI 2.65–3.86; $k = 19$) and low- and middle-income countries (3.38, 95% CI 2.44–4.69; $k = 25$; $p = 0.76$). It was also similar across world regions ($p = 0.69$), age groups ($p = 0.52$), care settings ($p = 0.30$), study sizes ($p = 0.47$) and cohort eras ($p = 0.29$), as detailed in Table 4 and illustrated in Figure 5. Estimates were smaller and homogeneous in cohorts in which bronchoscopy contributed to the diagnosis (2.64, 95% CI 2.33–2.99; I^2 0.0%) than in cohorts without

bronchoscopic diagnosis or with unreported criteria (3.54, 95% CI 2.75–4.56; I^2 77.7%; $p = 0.03$). This was the only nominally significant difference among 10 exploratory comparisons. Models that included post-injury mediators gave a somewhat smaller estimate than models that did not (2.85, 95% CI 2.03–4.01 versus 3.46, 2.73–4.38; $p = 0.33$). None of cohort mortality ($p = 0.31$), prevalence of inhalation injury ($p = 0.15$), burn size ($p = 0.35$), publication year ($p = 0.84$) or sample size ($p = 0.33$) explained a meaningful part of the heterogeneity.

Table 4. Subgroup analyses and meta-regression of the adjusted odds ratio.

Subgroup or moderator	k	Adjusted OR (95% CI)	I^2 (%)
Country income level (p for difference = 0.76)			
High-income	19	3.20 (2.65–3.86)	64.9
Low- and middle-income	25	3.38 (2.44–4.69)	76.3
Age group (p for difference = 0.52)			
Mixed ages	15	3.38 (2.44–4.66)	87.5
Adults	21	2.87 (2.19–3.75)	35.9
Children	4	3.79 (1.39–10.38)	5.6
Older adults	4	6.06 (0.89–41.19)	51.2
Care setting (p for difference = 0.30)			
ICU or major burns	20	2.99 (2.33–3.84)	66.9
All burn admissions	22	3.35 (2.45–4.59)	71.1
Emergency or prehospital cohort	2	4.54 (0.20–100.82)	0.0
Bronchoscopic confirmation (p for difference = 0.03)			
Bronchoscopy (all or some)	13	2.64 (2.33–2.99)	0.0
Non-bronchoscopic or not reported	31	3.54 (2.75–4.56)	77.7
Post-injury mediators in model (p for difference = 0.33)			
No mediators reported in model	27	3.46 (2.73–4.38)	70.0
Post-injury mediators in model	17	2.85 (2.03–4.01)	76.7
World region (p for difference = 0.69)			
Asia-Pacific	19	3.37 (2.47–4.60)	64.1
Europe	10	3.32 (2.10–5.25)	86.2
Africa, Middle East and Latin America	8	2.89 (1.54–5.42)	72.1
North America	7	3.75 (3.26–4.31)	0.0
Study size (p for difference = 0.47)			
500 patients or more	20	3.43 (2.71–4.34)	76.5
Fewer than 500 patients	24	2.98 (2.14–4.15)	62.4
Overall risk of bias (p for difference = 0.93)			
Moderate	21	3.15 (2.45–4.04)	82.4
High	22	3.36 (2.36–4.80)	49.4
Low	1	3.35 (2.30–4.89)	–
Data source (p for difference = 0.35)			
Multicenter	5	4.02 (2.02–7.98)	81.1
Single center	34	2.95 (2.31–3.76)	61.2
National registry or database	5	3.77 (2.35–6.04)	84.4
Cohort era (p for difference = 0.29)			
Cohort mid-point before 2010	8	3.72 (2.54–5.45)	85.7
Cohort mid-point 2010 or later	36	3.02 (2.39–3.82)	64.1
Meta-regression (ratio of ORs per unit; 95% CI; p; R^2)			
Cohort mortality (%)	42	0.993 (0.979–1.007); $p = 0.31$	R^2 6.8%
Inhalation injury prevalence (%)	34	0.991 (0.978–1.004); $p = 0.15$	R^2 8.5%
Mean or median burn size (%TBSA)	31	0.994 (0.980–1.008); $p = 0.35$	R^2 3.5%
Publication year	44	0.996 (0.959–1.035); $p = 0.84$	R^2 0.0%
log(sample size)	44	1.046 (0.954–1.148); $p = 0.33$	R^2 1.0%

Notes: Subgroup estimates from separate random-effects models within each subgroup (DerSimonian–Laird, Hartung–Knapp); p for difference from the test of subgroup differences. Meta-regression used restricted maximum likelihood with the Knapp–Hartung adjustment. CI, confidence interval; ICU, intensive care unit; k , number of cohorts; OR, odds ratio; TBSA, total body surface area.

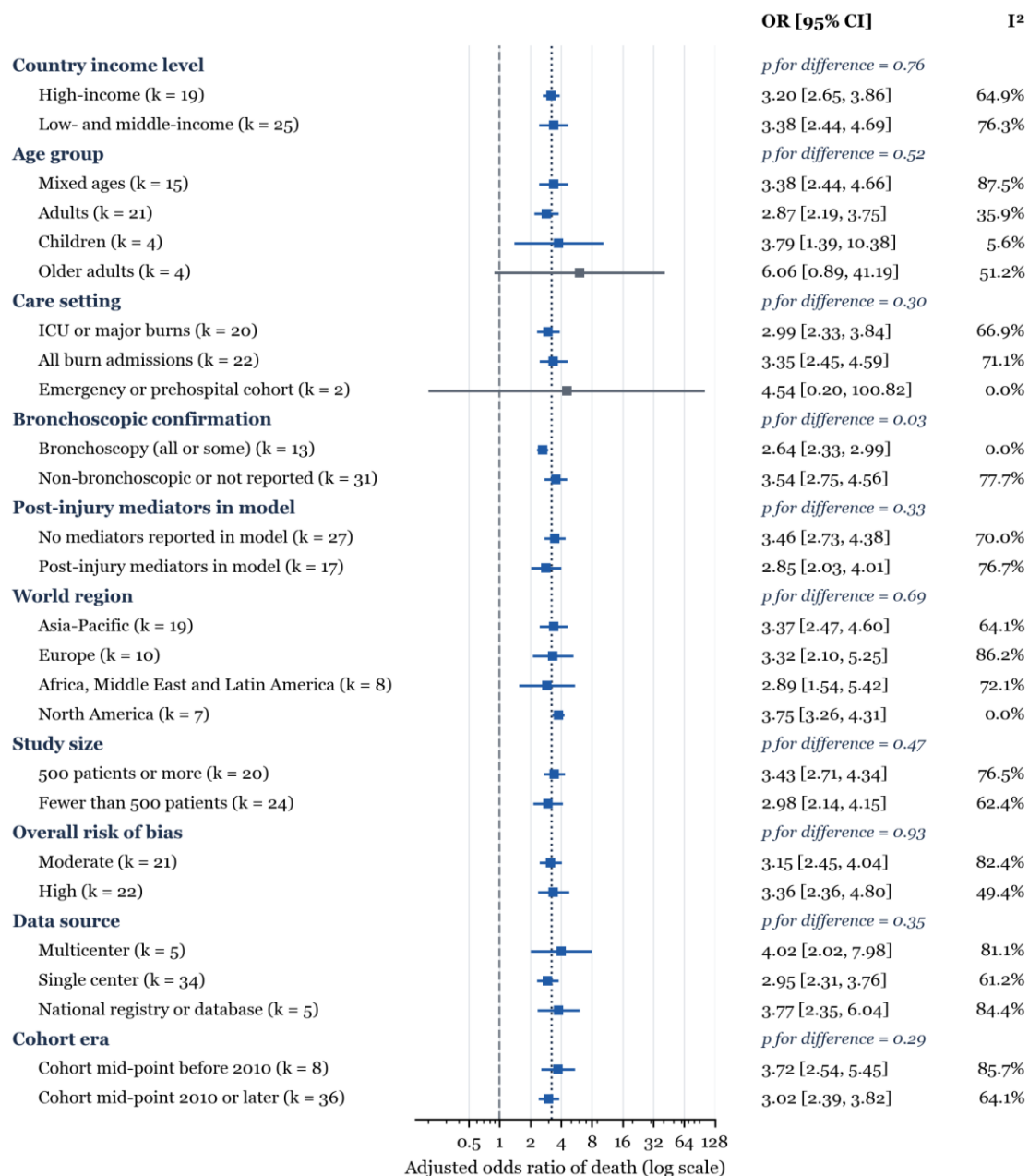


Figure 5. Subgroup analyses of the adjusted odds ratio of death for inhalation injury. Squares and lines show the random-effects estimate and 95% confidence interval within each subgroup; the dashed line marks OR = 1 and the dotted line the overall pooled estimate; the single cohort at low overall risk of bias (k = 1) is not shown; p values are from tests for subgroup differences. k, number of cohorts.

3.7. Sensitivity analyses

The pooled adjusted OR was stable across estimators (restricted maximum likelihood 3.23, 95% CI 2.67–3.91; Paule-Mandel 3.23, 2.66–3.92). It was also stable across exclusions, ranging from 3.02 when only full-text-assessed cohorts were included to 3.46 in models without mediators (Table 3). Restricting the analysis to cohorts at low or moderate risk of bias gave 3.16 (2.50–4.00) (k = 22); to full-text-assessed cohorts, 3.02 (2.43–3.75); and to models adjusted for both age and burn size, 3.04 (2.46–3.75). Leave-one-out estimates ranged from 3.12 to 3.36. One cohort was identified as influential;⁵¹ its exclusion gave 3.36 (2.81–4.03)

and reduced I² to 64.4%. Combining adjusted ORs and HRs gave 3.11, 95% CI 2.61–3.70 (k = 51).

3.8. Small-study effects and certainty of evidence

The funnel plot was symmetrical (Figure 6; Egger test *p* = 0.93; Begg test *p* = 0.58). Trim-and-fill imputed one study and left the estimate essentially unchanged (3.27, 95% CI 2.70–3.96). Certainty of evidence for the adjusted OR was moderate, downgraded once for risk of bias. It was not downgraded for inconsistency because the prediction interval lay entirely above 1, and not upgraded for a large effect because residual confounding could not be excluded. Certainty for the HR and crude estimates was low, as detailed in Table 5.

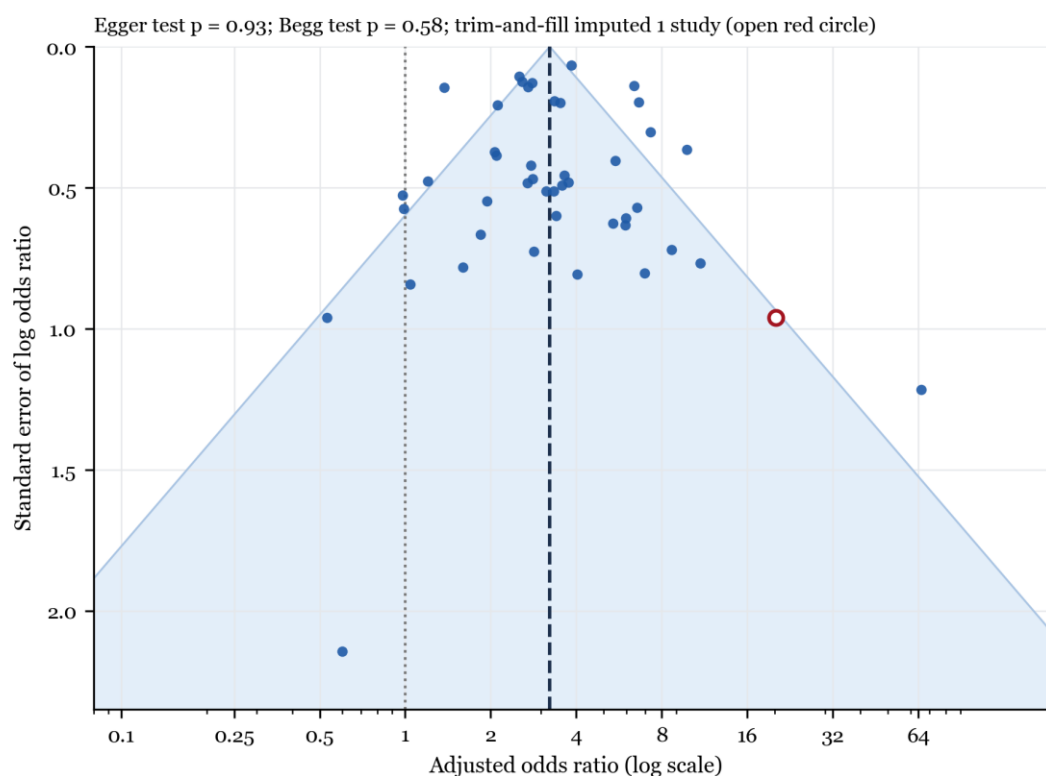


Figure 6. Funnel plot of the log adjusted odds ratios against their standard errors. The shaded area is the pseudo 95% confidence region around the pooled estimate (dashed line); the open red circle is the study imputed by trim-and-fill.

Table 5. Summary of findings and certainty of evidence (GRADE).

Outcome and measure	Studies (participants)	Pooled estimate (95% CI)	Certainty	Reasons
Inhalation injury and mortality, adjusted OR	44 cohorts; 332,465 patients	3.23 (2.67–3.90)	Moderate	Risk of bias (–1): half of the cohorts at high risk, mostly from few events per variable, data-driven variable selection and post-injury mediators. Not downgraded for inconsistency: I^2 72.3%, but the 95% prediction interval (1.43–7.30) did not include 1. Large-effect upgrade not applied because of residual confounding.
Inhalation injury and mortality, adjusted HR	7 cohorts	2.46 (1.45–4.19)	Low	Risk of bias (–1); imprecision and few studies (–1).
Inhalation injury and mortality, crude OR	27 cohorts; 35,566 patients	9.45 (6.40–13.95)	Low	Confounding by burn size and age (–1); inconsistency, I^2 89.2% (–1).

Notes: Certainty rated with the GRADE approach for prognostic factor research, starting at high for cohort studies. CI, confidence interval; HR, hazard ratio; OR, odds ratio.

4. Discussion

4.1. Principal findings

This meta-analysis of 53 cohorts, 44 of which contributed adjusted ORs from 332,465 patients, found that smoke inhalation injury was associated with about threefold higher odds of death after adjustment for burn size, age and other predictors (OR 3.23, 95% CI 2.67–3.90). The direction of the association was consistent, and the 95% prediction interval excluded 1. The estimate held up under every choice of estimator and every pre-specified exclusion. Adjusted hazard ratios pointed the same way. These estimates describe independent prognostic value. They are conditional on the covariates of each model, and those models were built to predict death, not to estimate the causal effect of inhalation injury. They do not imply that preventing or treating inhalation injury would lower mortality by the same amount.

The crude comparison is the figure most often quoted at the bedside, and it greatly overstates this independent weight. In the cohorts that reported both measures, adjustment reduced the OR from about 9.61 to about 2.92. That is roughly 0.30 times the crude OR. The attenuation was about 70%. Patients with inhalation injury tend to have larger, deeper flame burns and to be older, and these factors explain much of their excess

mortality. Even so, a residual threefold increase is clinically important.

4.2. Comparison with previous studies

These findings extend recent syntheses that covered parts of the question. The pediatric meta-analysis, based mainly on case-control studies, reported an OR of 5.0 for inhalation injury,³⁰ closer to the crude than to the adjusted estimates found here. The four pediatric cohorts with adjusted ORs in the present review gave 3.79 (1.39–10.38) with little heterogeneity. This suggests that, once burn size is accounted for, the relative effect in children resembles that in adults. A recent meta-analysis in older adults reported a pooled risk ratio of 2.95 for death with inhalation injury.³¹ The four older-adult cohorts here gave a larger but imprecise adjusted OR of 6.06 (0.89–41.19). The two figures cannot be compared directly, because mortality is high in older patients and ORs then lie further from 1 than risk ratios. The present estimate for this group is too imprecise to show whether the relative effect differs from that in younger patients. The test for differences between age groups was not significant ($p = 0.52$). Because only the adjusted coefficients reported within each cohort were pooled, the analysis shows that inhalation injury remains an independent predictor across age groups. Its effect is smaller than crude comparisons imply but clearly

above the null. The review adds a separate synthesis of hazard ratios, individual reporting of risk ratios, a direct within-cohort measure of attenuation and a comparison between income groups. Earlier syntheses offered none of these. The two recent reviews of bronchoscopic grading addressed severity among patients who all had inhalation injury, so their results complement rather than overlap the present question.^{32,33}

4.3. Clinical and biological plausibility

The association has a clear biological basis. Heated gases and toxic smoke cause airway edema and obstruction, loss of ciliary clearance, cast formation and alveolar injury. Carbon monoxide and cyanide add systemic hypoxia. Early endothelial injury and fibrinolytic abnormalities have been documented in patients with inhalation injury,^{9,10} and these may increase capillary leak and fluid retention.¹¹ A higher risk of nosocomial pneumonia and ARDS offers a route to late deaths.^{12,14} Some of these complications lie on the causal path between inhalation injury and death. Models that adjusted for them therefore estimated a direct, not a total, effect, which fits the smaller estimate seen in such models. At admission, the total effect is the more relevant quantity for triage, and it is estimated by models without post-injury mediators (3.46, 95% CI 2.73–4.38).

Respiratory complications could not be synthesized as outcomes, because only two cohorts reported adjusted estimates for them. This gap matters directly to pulmonology. Pneumonia and ARDS are likely intermediate steps between inhalation injury and death. Future cohorts should report them with the same multivariable rigor as mortality.

4.4. Interpretation of heterogeneity

Heterogeneity was considerable, but it concerned mainly the magnitude of the effect, not its direction. Part of it is inherent to prognostic factor meta-analysis. The adjusted ORs came from models with different covariates, different coding of burn size (continuous, categorical or within composite scores) and different variable-selection methods, so they do not strictly estimate the same parameter. The random-effects model and the prediction interval were used to accommodate this, not to hide it.

Diagnostic definitions are another probable source. The prevalence of inhalation injury ranged from 0.3% to 73.3% across cohorts, a spread that reflects diagnostic thresholds as well as case mix. Cohorts in which bronchoscopy contributed to the diagnosis gave a smaller, homogeneous estimate. Those without bronchoscopic diagnosis, or with unreported criteria, were more variable. This was one of 10 exploratory comparisons. It should be regarded as hypothesis-generating. It fits misclassification in both directions: clinical diagnosis may capture mainly severe cases with obvious facial burns and carbonaceous sputum, whereas coding may miss mild injury.^{16,18,19} Differences in case mix between intensive care and all-admission cohorts may contribute further. Neither cohort mortality nor burn size explained the variation. These moderators were tested in exploratory analyses with few cohorts per group, so the relative effect may be similar across settings, but this review cannot show it.

How inhalation injury is recorded also differs systematically between data sources. National registries and administrative databases rely on a single coded field, completed by different clinicians with different thresholds. One large registry did not record inhalation status for many survivors.³⁷ Single-center cohorts in low- and middle-income countries more often used clinical criteria alone, because bronchoscopy was unavailable or reserved for intubated patients. Such differences may add noise rather than a consistent bias, and the similar pooled estimates for registry, multicenter and single-center cohorts are compatible with this, although the number of cohorts per group is small. A standardized minimum definition would still

make future estimates more comparable, for example exposure in an enclosed space with at least one objective sign, or bronchoscopic confirmation when available.

The pooled adjusted hazard ratio (2.46) and the two adjusted risk ratios (2.08 and 2.35)^{86,87} were smaller than the pooled adjusted OR. The measures themselves explain this difference. It does not indicate a weaker effect in those cohorts. Death was common among patients with inhalation injury (37.5% in the cohorts that reported death counts). When an outcome is common, the OR lies further from 1 than the corresponding risk ratio. Hazard ratios also depend on the timing of death and on the length of follow-up, which differed between cohorts. For these reasons the measures were analyzed separately: ORs and HRs were pooled, and the two RRs were reported individually. The analysis combining ORs and hazard ratios served only as a sensitivity analysis. The pooled OR is a measure of relative odds, not a threefold increase in risk. The absolute translations given below are the better basis for clinical communication.

4.5. Absolute risk and resource-limited settings

The relative effect can be translated into absolute terms, with the caveat that ORs apply only to a stated baseline risk and are conditional on the other covariates. Mortality was 5.7% in patients without inhalation injury in the cohorts with death counts. Applied to that baseline (odds = risk/[1 – risk]), an adjusted OR of 3.23 corresponds to a mortality of about 16% in otherwise comparable patients with inhalation injury. For a patient whose burn size and age imply a baseline risk of 20%, as is common in intensive care cohorts, the corresponding risk rises to about 45%. These are illustrations, not predictions for individual patients. Even so, differences of this size are large enough to change triage category, the intensity of monitoring and the timing of transfer to a burn center.

The relative effect was similar in low- and middle-income and high-income countries. It is a reasonable inference, though not a direct result of this review, that a similar OR translates into a larger absolute excess of deaths where baseline mortality is higher because burn care resources are limited.^{5,6,88} In the present data, median cohort mortality was similar in the two income groups (16.4% and 17.0%), so the inference rests on external population data.

In Indonesia, bronchoscopy, protective ventilation and burn intensive care are, in the authors' observation, concentrated in a few referral centers. The included cohort from the national referral burn center in Jakarta, in which bronchoscopy contributed to the diagnosis, found an adjusted OR close to the pooled estimate.⁶⁰ A recent review of physical findings for inhalation injury in rural and low-resource settings concluded that dyspnea, stridor and hoarseness were the most useful signs when bronchoscopy is unavailable.³⁴ Identifying inhalation injury from history and physical findings should therefore prompt early airway assessment, measurement of carboxyhemoglobin and timely referral. The present estimate supports including inhalation injury in the revised Baux score and newer prediction tools,^{26–28} although its weight should be recalibrated locally.

4.6. Weight of inhalation injury in prognostic scores

The pooled estimate can also be placed on the scale used by burn mortality scores. In the included models that reported age per year, each additional year carried an adjusted OR of about 1.08 to 1.13.^{36,45,52} On that scale, the pooled OR of 3.23 for inhalation injury corresponds to roughly 10 to 15 additional years of age. This is of the same order as the 17 points that the revised Baux score adds for inhalation injury, a weight equivalent to 17 years of age or 17% of total body surface area. The present synthesis is therefore compatible with the magnitude of that weight, which was originally derived from a single large registry,⁸⁹ using data from many

settings. Recent validations in Ethiopia and Uganda reported excellent discrimination of the revised Baux score.^{26,27} An Indian cohort found that it overestimated observed mortality.²⁹ A machine-learning score derived from the German Burn Registry also performed strongly.²⁸ Local recalibration of the weight for inhalation injury, ideally together with a standardized diagnosis, may therefore matter more for calibration than the addition of new predictors.

Cohort era did not modify the association. Burn care has changed over the period covered by the included cohorts, yet inhalation injury has remained a strong predictor in recent ones, so improvements in burn care appear not to have removed its excess risk. This agrees with the limited and still evolving evidence for injury-specific treatments.^{21–23}

4.7. Implications for internal medicine and critical care

The findings are relevant to internal medicine, pulmonology and critical care, because patients with inhalation injury are often first assessed in emergency departments and general intensive care units, not in burn centers. Several components of care are linked directly to the mechanisms through which inhalation injury increases mortality: early measurement of carboxyhemoglobin and lactate, consideration of cyanide toxicity in patients with smoke exposure and unexplained lactic acidosis,²⁴ anticipation of airway edema, lung-protective ventilation, and attention to ventilator-associated pneumonia, which is more frequent after inhalation injury.^{12,13} Survivors also have higher rates of post-discharge pulmonary sequelae, including ineffective airway clearance, respiratory infections and dyspnea,⁹⁰ so pulmonary follow-up is warranted even when the cutaneous burn is small.

4.8. Strengths and limitations

This review has several strengths. It was restricted to multivariable-adjusted estimates and kept odds, hazard and risk ratios apart. It combined four databases with citation searching. It applied explicit rules for overlapping populations and implausible estimates, and every estimate was checked against its source report. The within-study comparison of crude and adjusted estimates also quantified confounding directly, rather than inferring it from between-study regression.

Several limitations must be considered. First, all studies were observational and their models were built for prediction, so residual confounding by burn depth, comorbidity and treatment intensity is likely. Second, adjustment sets varied, and a third of the models included post-injury mediators that attenuate the association. Third, the diagnosis of inhalation injury was not standardized; it was registry-coded, clinical or unreported in most cohorts. Fourth, about half of the cohorts were at high risk of bias, mostly because of few deaths relative to candidate predictors and data-driven variable selection, which tends to inflate retained coefficients.

Fifth, more than a third of the reports sought could not be retrieved, and some estimates came from abstracts or were converted from logistic coefficients, although sensitivity analyses excluding them changed little. Embase and Web of Science were not searched, and the protocol was not registered. Sixth, studies in which inhalation injury was only an adjustment covariate were excluded by design. Such coefficients often come from large, fully adjusted registry models, so their exclusion could have shifted the estimate in either direction. Seventh, and probably most important, 20 reports entered inhalation injury into a model but did not retain or report it. Funnel-plot methods cannot detect this selective reporting of predictors, which would bias the pooled estimate upward. The symmetrical funnel plot should not be over-interpreted. Finally, a small residual overlap between single-center cohorts and national registries cannot be excluded, although the largest overlapping reports were removed.

4.9. Implications for practice and research

For clinical practice, inhalation injury should be documented at admission with explicit criteria. It should be weighed together with burn size and age in triage, airway planning, referral and discussions with families. Documentation comes first. For research, burn registries and cohort studies should report the full multivariable model, including the coefficient for inhalation injury whether or not it is significant. They should distinguish predictors measured at admission from later complications and adopt a standardized diagnostic and grading definition. Trials of airway-directed therapy^{22,23} and studies of long-term pulmonary sequelae in survivors⁹⁰ would benefit from the same standardization. Individual participant data from large registries would allow the total and direct effects of inhalation injury to be estimated with a common set of covariates.

5. Conclusion

Smoke inhalation injury was an independent predictor of death in hospitalized burn patients. Across 44 cohorts it was associated with about threefold higher adjusted odds of death (OR 3.23, 95% CI 2.67–3.90), and adjusted hazard ratios agreed. Within the same cohorts, the adjusted association was about 0.30 times the crude one, because patients with inhalation injury also have larger burns and are older. The association persisted. It survived every sensitivity analysis, and its prediction interval excluded 1. The relative effect was similar in high-income and low- and middle-income countries, which, if baseline mortality is higher, would imply a larger absolute burden (this was not measured here). Inhalation injury should remain a core element of early burn triage, risk adjustment and referral decisions, including where bronchoscopic diagnosis is unavailable. Heterogeneity limits the precision of current estimates. Standardized diagnostic criteria and complete reporting of multivariable models in burn registries and cohort studies are needed to reduce it.

Declarations

Ethics approval and consent to participate

Ethical approval and informed consent were not required, because this study analyzed only previously published aggregate data and no new data were collected from human participants.

Consent for publication

Not applicable. This study analyzed only previously published aggregate data and contains no individual person's data.

Use of artificial intelligence

The authors did not use generative artificial intelligence in the preparation of this manuscript.

Author contributions

Conceptualization: H.L.Y. and Y.S.S. Methodology, data curation and formal analysis: H.L.Y. Writing – original draft: H.L.Y. Writing – review & editing: H.L.Y. and Y.S.S. Supervision: Y.S.S. Both authors approved the final manuscript and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors have no financial or non-financial competing interests to declare.

Data availability

Data are available from the corresponding author on reasonable request.

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