Research Article

Ventilation practices in burn patients—an international prospective observational cohort study

Marcus J. Schultz1, Janneke Horn1, Markus W. Hollmann1, Benedikt Preckel1, Gerie J. Glas1,*, Kirsten Colpaert2, Manu Malbrain3,29, Ary Serpa Neto4,20,21, Karim Asehnoune5, Marcello Gamma de Abreu6, Ignacio Martin-Loeches7, Paolo Pelosi8, Folke Sjöberg9, Jan M. Binnekade1, Berry Cleffken10, Nicole P. Juffermans1, Paul Knape11, Bert G. Loe12, David P. Mackie11, Perenlei Enkhbaatar13, Nadia Depetris14, Anders Pemer15, Eva Herrero16, Lucia Cachafeiro16, Marc Jeschke17, Jeffrey Lipman18, Matthieu Legrand21,36, Johannes Horter22, Athina Lavrentieva23, Gerie Glas1,*, Alex Kazemi24, Anne Berit Gutormsen25, Frederik Huss26, Mark Kol27, Helen Wong27, Therese Starr28, Luc De Crop2, Wilson de Oliveira Filho29, João Manoel Silva Junior30, Cintia M.C. Grion31, Marc G. Jeschke32, Marjorie Burnett32, Frederik Mondrup15, Francois Ravat33, Mathieu Fontaine33, Karim Asehoun34, Renan Le Floch34, Mathieu Jeanne35, Morgane Bacus35, Maïté Chaussard36, Marcus Lehnhardt37, Bassem Daniel Mikhail37, Jochen Gille38, Aidan Sharkey7, Nicole Trommel10, Auke C. Reindinga12, Nadine Vlieleurs11, Anna Tilsley24, Henning Onarheim25, Maria Teresa Bouza39, Alexander Agrifoglio16, Filip Fredén26, Tina Palmieri40, Lynda E. Painting40 and LAMiNAR investigators

1Academic Medical Center, University of Amsterdam, Amsterdam, AZ 1105, The Netherlands, 2Ghent University Hospital, Ghent 9000, Belgium, 3Vrije Universiteit Brussel, Brussel, Jette 1090, Belgium, 4ABC Medical School, São Paulo, Bangú, SP 5001, Brazil, 5Service d’Anesthésie Réanimation Chirurgicale, Nantes 44093, France, 6University Hospital Carl Gustav Carus, Dresden 01307, Germany, 7St James University Hospital, Dublin D08 NHY1, Ireland, 8University of Genoa, Genoa, GE 16128, Italy, 9Linköping University Hospital, Linköping 581 85, Sweden, 10Maasstad Hospital, Rotterdam, DZ 3079, The Netherlands, 11Red Cross Hospital, Beverwijk, LE 1942, The Netherlands, 12Martini Hospital, Groningen, NT 9287, The Netherlands, 13University of Texas Medical Branch, Galveston, TX 77555, USA, 14Turin CTO Burn Center, Turin, TO 10126, Italy, 15Rigshospitalet, Copenhagen 2100, Denmark, 16La Paz University Hospital, Madrid 28046, Spain, 17Ross Tilley Burn Centre, Sunnybrook Health Sciences Centre, Toronto M4N 3M5, Canada, 18Royal Brisbane and Women’s Hospital, Queensland University, Herston, QLD 4029, Australia, 19Department of Critical Care Medicine, Hospital Israelita Albert Einstein, São Paulo 05652-900, Brazil, 20Australian and New Zealand Intensive Care Research Centre. Monash University, Melbourne, VIC 3004, Australia, 21GH St-Louis- Lariboisière, APHP, Paris 75010, France, 22BG Klinik Ludwigshafen, Ludwigshafen 67071, Germany, 23Papanikoalou Hospital, Thessaloniki 546 21, Greece, 24Middlemore Hospital, Otahuhu, Auckland 2025, New Zealand, 25Haukeland University Hospital, Bergen 5021, Norway and 26Uppsala University Hospital, Uppsala 751 85, Sweden, 27Concord Repatriation General Hospital NSW, University of Sydney, Concord 2139, Australia, 28Ziekenhuis Netwerk Antwerpen–Stuivenberg,
Burn patients often suffer from inhalation trauma. Both thermal and inhalation trauma may result in respiratory dysfunction, necessitating MV [12–14]. Whether lung-protective ventilation is applied in burn patients is yet unknown. There are no evidence-based guidelines for MV in burn patients. Furthermore, it is unknown whether this specific population

Background: Mechanical ventilation (MV) is considered a lifesaving intervention, but it also causes lung injury [1,2]. Ventilator settings important in ‘ventilator-induced lung injury’ (VILI) include tidal volume ($V_T$) and positive end-expiratory pressure (PEEP). To limit VILI, ‘lung-protective’ MV strategies have become standard care in the general intensive care unit (ICU) [3,4]. $V_T$ sizes of ≤8 mL/kg predicted body weight (PBW) are preferred [3,4] as patients with and without acute respiratory distress syndrome (ARDS) benefit from low $V_T$ [1,5–8]. Current guidelines suggest the use of higher PEEP (e.g., >10 cmH$_2$O) for patients with moderate to severe ARDS [9,10]. The optimal PEEP for patients without ARDS remains debatable. However, a trend towards the use of moderate PEEP, generally between 5 and 10 cmH$_2$O, has been reported [4,11].
benefits from lung-protective ventilation as data on the association between ventilation practices and clinical outcomes are scant [15].

To determine ventilation practices in burn ICUs worldwide we performed an international prospective observational cohort study entitled ‘Local Assessment of MaNAge ment in BuRn Patients’ (LAMiNAR). We expected extensive variability in ventilation practices. The secondary objective was to determine the association between ventilation settings, focusing on \( V_T \) size and levels of PEEP, and duration of ventilation in burn patients, with the number of ventilator-free days and alive at day 28 (VFD-28) as the primary outcome measure.

Methods

Design

The LAMiNAR study is a prospective observational international cohort study in specialized burn ICUs. Burn patients were included during a 3-month period per participating center. The study protocol was centrally approved by the Institutional Review Board (IRB) of the Academic Medical Center at the University of Amsterdam, The Netherlands (W14_314#15.0178). Locally, ethical approval was obtained in compliance with the local regulatory requirements. If applicable, written informed consent from individual patients or legal representatives was obtained prior to enrollment. The study was registered at www.clinicaltrials.gov (NCT02312869). National coordinators were appointed in participating countries (see online supplementary appendix, Table 2); they recruited collaborating centers and assisted local coordinators.

Study population

Consecutive adult (≥18 years) burn patients admitted to a participating burn ICU who needed invasive MV, irrespective of severity of burn injury or presence of inhalation trauma, were eligible for inclusion. There were no exclusion criteria.

Data collection

Patient characteristics and baseline data were collected on the day of ICU admission: Simplified Acute Physiology Score (SAPS) II, Lung injury scores (LIS) [16] and Sequential Organ Failure Assessment (SOFA) scores [17]; data on etiology and severity of burn injury or presence of inhalation trauma, severity of burn injury (e.g. percentage of total body surface area burned (TBSA %); presence of inhalation trauma: not suspected, clinical diagnosis, or bronchoscopically confirmed; severity of inhalation trauma graded as mild (i.e. minor or patchy areas of erythema, carbonaceous deposits in bronchi), moderate (i.e. moderate degree of erythema, carbonaceous deposits, bronchorrhea, or bronchial obstruction) or severe (i.e. severe inflammation with friability, copious carbonaceous deposits, bronchorrhea, obstruction or evidence of mucosal sloughing, necrosis or obliteration) [18]. Data on the timing of bronchoscopy and applied nebulization protocols (e.g. use of nebulized heparin, mucolytics or bronchodilators) were not collected.

For MV parameters, day 0 was defined as the first day of MV in the ICU. Ventilator data (described below) and clinical outcome parameters were collected daily until day seven, death or discharge from ICU, whichever came first. All ventilatory data were single measurements collected at the same time point. Daily data were collected from the morning round if the patient was stable for at least 1 h; i.e. closest to 08:00 am, otherwise data from 1 h earlier or later was collected. Whether a patient was considered stable was left at the discretion of the attending physician.

Clinical outcome parameters included: VFD-28, a VFD was defined as a period of 24 consecutive hours in which the patient was alive and without MV, in hospital and ICU length of stay (LOS) and all-cause mortality. Other outcome parameters included: development of pneumonia (i.e. new or progressive radiographic infiltrate plus at least two of the following: fever >38°C, leukocytosis, leucopenia and/or purulent secretions) [4] or ARDS according to the Berlin definition [19] and development of acute renal failure according to acute kidney injury network criteria [20]. Data on the duration of MV, LOS and mortality (in ICU and hospital) were assessed on days 28 and 90. We also collected data on: \( \text{PaO}_2/\text{FiO}_2 \) ratio (mmHg), respiratory rate (breaths per minute), minute ventilation and arterial blood gas (\( \text{P}_a\text{CO}_2 \), \( \text{pH} \), bicarbonate).

Ventilatory data included: \( V_T \), PEEP, \( \text{FiO}_2 \), ventilator mode (e.g. high-frequency ventilation, spontaneous or controlled modes), peak airway pressure \( (P_{\text{peak}}) \) and plateau pressure \( (P_{\text{plat}}) \) for volume-controlled ventilation; maximum airway pressure \( (P_{\text{max}}) \) for pressure-controlled ventilation; and driving pressure [calculated as \( P_{\text{plat}} \) (or equivalent) minus PEEP] [21].

Anonymized patient data were entered into a web-based, password-secured, electronic case record form (Openclinica, Boston, MA, USA).

Study objectives and parameters

The objective of this study was to determine current ventilation practices in burn patients. The main ventilatory parameters were \( V_T \) and PEEP. Secondary ventilatory parameters included \( \text{FiO}_2 \), ventilator mode, \( P_{\text{peak}} \) and \( P_{\text{plat}} \) for volume-controlled ventilation; \( P_{\text{max}} \) for pressure-controlled ventilation; and driving pressure. The main outcome parameter was number of VFD-28.

Sample size and statistical analysis

We aimed to include 300 patients to enable a multivariate analysis to determine the association between ventilator settings and number of VFD-28. A sample size of 300 patients was required to have a power of 0.80, with a significance level of 0.05, using an estimated effect size of 0.40 [22], while using four independent variables (i.e. \( V_T \), PEEP, \( \text{FiO}_2 \) and ventilator
mode) in the model. Inclusion in the 3-month period per participating center was much lower than expected. Therefore, we decided to deviate from our originally planned analysis for our secondary objective, and only analyzed the association between one ventilatory parameter (VT) and the number of VFD-28. We did not analyze the association between levels of PEEP and the number of VFD-28 as only five patients were ventilated with high PEEP levels (i.e. > 10 cmH2O).

Continuous not normally distributed variables were expressed by medians and interquartile ranges (IQRs). Categorical variables were expressed as n (%). Groups were compared with the Mann–Whitney U test. Categorical variables were compared with the Chi–square or Fisher’s exact tests.

VT was presented as volume normalized for PBW (mL/kg PBW) [5]. Patients in whom PBW could not be calculated were omitted from the analysis. We used scatterplots to present distributions of VT vs PEEP, VT vs respiratory rate, VT vs FiO2 and VT vs Pmax. Widely accepted cut-off values of 8 mL/kg PBW for VT, 14 breaths per min for respiratory rate, 5 cmH2O for PEEP, 0.6 for FiO2 and 30 cmH2O for Pmax, were used to form the matrices [4].

In a post hoc analysis we evaluated differences in ventilation management between patients with and without inhalation trauma, and analyzed the association between the presence of inhalation trauma and number of VFD-28. Patients were stratified into two groups based on the presence [defined as any suspected (clinical diagnosis) or bronchoscopically confirmed inhalation trauma] or absence of inhalation trauma.

We presented ventilation settings for all patients and compared ventilation management between patients with and without inhalation trauma, focusing on the first day of ventilation (day 1).

The median VT on the first day of ventilation was used to determine whether ventilation was ‘lung-protective’ (low VT): ≤ 8 mL/kg PBW; VT > 8 mL/kg PBW was considered as non-protective (high VT).

The association between (1) VT size (VT ≤ 8 vs VT > 8 mL/kg PBW) and (2) inhalation trauma and the number of VFD-28 was analyzed using a competing risk model with death before extubation as competing risk. Data were presented with cumulative incidence curves. The subdistribution hazard ratio for VT and inhalation trauma were calculated using a Cox proportional hazards model, and Schoenfeld residuals were used to test the proportional hazard assumption [23]. Duration of ventilation in survivors was compared using median difference from a quantile regression.

We made no assumptions for missing data and did not adjust for multiplicity across analyses. Patients that were enrolled without subsequent data entry (e.g. no daily data collection and no follow-up data) were excluded from analysis. Statistical significance was considered at p < 0.05. All analyses were performed with R v.2.12.0 (http://www.r-project.org).

### Results

#### Patients

Patients were enrolled between September 2015 and April 2017. In total, 28 specialized burn ICUs in 16 countries participated (see online supplementary appendix Tables 1 and 2). Patient recruitment was lower than expected. Although we expected to include 300 patients within the 3-month periods, only 170 patients were enrolled, of which 160 patients could be included in the analysis (see online supplementary appendix Figure S1).

Demographic, baseline and etiological characteristics are presented in Table 1. The median percentage of TBSA was 25% (IQR 10–40). Inhalation trauma was clinically suspected in 84 out of 159 patients (52.8%) (1 patient

### Table 1. Patient characteristics and severity of burn injury

| All n = 160 | With inhalation trauma n = 84 | Without inhalation trauma n = 75 | P value |
|-------------|-----------------------------|---------------------------------|---------|
| Gender, male, n (%) | 119 (75%) | 64 (76%) | 55 (73%) | 0.82 |
| Age (years) | 46 (30–60) | 48 (30–60) | 44 (29–58) | 0.48 |
| Height (cm), n | 175 (167–180), 150 | 175 (166–180), 81 | 174 (167–180), 69 | 0.58 |
| Weight (kg), n | 80 (70–90), 158 | 80 (70–90), 84 | 80 (72–90), 74 | 0.68 |
| SAPS II | 48 (35–60) | 49 (37–62) | 43 (35–57) | 0.08 |
| LIS | 0.75 (0.33–1.33) | 1 (0.33–1.5) | 0.75 (0.27–1.25) | 0.16 |
| SOFA (total) | 9 (8–10) | 9 (8–11) | 8 (7–10) | 0.09 |
| Type of burn injury*, n (%) | | | | |
| Flames or explosion | 137 (86.2%) | 75 (89.3%) | 62 (82.7%) | |
| Scalds or steam | 5 (3.1%) | 2 (2.3%) | 3 (4%) | |
| Contact burns | 5 (3.1%) | 0 | 5 (6.7%) | |
| Other | 12 (7.5%) | 7 (8.3%) | 5 (6.7%) | 0.10 |
| TBSA (%) | 97 (60.6%) | 50 (59.5%) | 47 (62.6%) | 0.68 |

*One patient had no data.

LIS lung injury score at admission, n number of patients, SAPS II simplified acute physiology score, SOFA sequential organ failure assessment, TBSA total body surface area of burn.
had no data available on the presence of inhalation trauma) and was confirmed by bronchoscopy in 45 of these patients (53.6%). Bronchoscopically confirmed inhalation trauma was graded as mild, moderate or severe in respectively 16, 18 and 11 patients. The number of surgical procedures performed in the first day of mechanical ventilation was similar between patients with and without inhalation trauma and included burn wound excisions, performed in 9 patients, debridement (n = 7) and escharotomy (n = 4).

**Ventilator settings**

Low V\textsubscript{T} were used in 74% of the patients (Table 2, Figures 1 and 2). The median V\textsubscript{T} size was 7.3 (IQR 6.2–8.3) mL/kg PBW for all patients and did not differ significantly between patients with and without inhalation trauma (p = 0.58; Table 2). V\textsubscript{T} sizes were similar between patients with clinical and bronchoscopically confirmed diagnosis of inhalation trauma, irrespective of the severity of inhalation trauma (p = 0.31). Median V\textsubscript{T} size was significantly higher in patients ventilated with spontaneous [V\textsubscript{T} 8 mL/kg PBW (IQR 7.3–9.5)] compared to controlled ventilation modes [V\textsubscript{T} 7 mL/kg PBW (IQR 6.1–8), p = 0.007].

All patients were ventilated with PEEP of 5 cmH\textsubscript{2}O or higher, and patients with inhalation trauma received higher PEEP compared to patients without inhalation trauma [median 8 cmH\textsubscript{2}O (IQR 5–10) vs 5 cmH\textsubscript{2}O (IQR 5–8); p = 0.004; Table 2]. The median FiO\textsubscript{2} did not differ between groups (Table 2). Controlled modes of ventilation were applied more frequently, with no significant differences in type of ventilator mode used for patients with or without inhalation trauma (Table 2). High-frequency ventilation was applied in 2 patients, both with inhalation trauma. P\textsubscript{max} values <30 cmH\textsubscript{2}O were used in 80% of patients (Figure 1b). Median P\textsubscript{peak} was significantly higher in inhalation trauma patients compared to patients without inhalation trauma [31 cmH\textsubscript{2}O (IQR 23–35) vs 20 cmH\textsubscript{2}O (IQR 17–25), p < 0.001]. Driving pressure did not differ between patients with and without inhalation trauma [14 cmH\textsubscript{2}O (IQR 11–18) vs 13 cmH\textsubscript{2}O (IQR 10–16), p = 0.55] and was <15 cmH\textsubscript{2}O in 59% of patients (Figure 1d and Table 2). Ventilatory data over
Clinical outcomes
The median number of VFD-28 was 17 (IQR 0–26) and did not differ significantly between patients ventilated with $V_T \leq 8$ mL/kg PWB compared to $V_T > 8$ mL/kg PWB. The subdistribution hazard ratio for extubation in patients ventilated with $V_T \leq 8$ mL/kg PWB while considering death as a competing risk was $0.99 (0.63–1.57), p = 0.98$ (Figure 3 and online supplementary appendix Table 3).

Patients with inhalation trauma had fewer VFD-28 compared to patients without inhalation trauma [16 (IQR 0–26) vs 21 (IQR 0–26)], with a subdistribution hazard ratio for extubation in inhalation trauma patients of 0.61 (0.42–0.82; $p = 0.01$), considering death before extubation as a competing risk (see online supplementary appendix Table S3 and Figure S3). Hence, patients with inhalation trauma had a 39% lower probability of being successfully liberated from MV by day 28 when compared to patients without inhalation trauma. This difference is primarily driven by the longer duration of MV ($p = 0.02$) rather than a
higher mortality ($p = 0.70$, see online supplementary appendix Table S3).

Pneumonia was diagnosed significantly more often in patients with inhalation trauma (see online supplementary appendix Table S4). Most pneumonias occurred in the first week of ICU admission (53 out of 59 patients), and were diagnosed while the patient was mechanically ventilated (56 out of 59 patients). Pneumonia was microbiologically confirmed in 20 out of 38 patients with inhalation trauma vs 11 out of 21 patients without inhalation trauma. ARDS was reported in 28 out of 160 patients; the incidence of ARDS did not differ significantly between patients with and without inhalation trauma. The LOS in the ICU, or in hospital, and 90-day mortality did not differ between groups (see supplementary appendix Table 4).

**Discussion**

This international prospective observational study investigated ventilation practices in specialized adult burn ICUs. It is one of the largest prospective cohort studies in this specific patient population over a short timeframe.

Ventilation practices in critically ill burn patients were less variable than expected as about three-quarters of the patients were ventilated with low $V_T$, irrespective of the presence of inhalation trauma. Use of PEEP between 5 and 10 cmH$_2$O...
and P_{max} values <30 cmH_{2}O have also been largely adopted. This suggests that lung-protective ventilation strategies are implemented in burn patients. We found no difference in VFD-28 between patients ventilated with low compared to high V_{T}.

The V_{T} in our study was marginally lower than reported V_{T} in nonburn patients without or at risk for ARDS [4] or ARDS patients [3]. The implementation of low V_{T} in the majority of patients in our study contrasts with a survey on mechanical ventilation practices amongst North American burn centers conducted in 2014. The American survey showed that ventilation practices tended to deviate from lung-protective strategies as only 26% of the respondents adhered to the ARDSNet protocol in burn patients with severe ARDS [24]. A systematic review on MV in burn patients showed a high variability in MV practices with a trend towards implementation of lung-protective settings in recent years [15]. Indeed, V_{T} declined from 14 mL/kg in studies performed before 2006 to ~8 mL/kg in more recent studies [15]. In our study, applied V_{T} did not differ between patients with or without inhalation trauma. However, patients with inhalation trauma were ventilated with significantly higher PEEP and P_{max}. This was also seen in the systematic review on applied MV strategies in burn patients [15], where the majority of studies reported PEEP levels of up to 10 cmH_{2}O. Higher PEEP levels were frequently used in studies including patients with inhalation trauma [15]. Also, studies conducted in the last decade reported the use of lower P_{max} values when compared to earlier studies [15]. In the present study, P_{plat} values were only reported for a few patients. We used P_{max} as a surrogate parameter for P_{plat} to calculate driving pressures [21]. Consequently, the calculated driving pressure could be an overestimation of the actual driving pressure. Still, driving pressures did not differ significantly between groups and were within suggested safety limits [3,25,26]. Finally, in our study, applied FiO_{2} did not differ significantly between patients with and without inhalation trauma and medians were comparable to FiO_{2} applied to critically ill patients without ARDS [4]. Currently, there are no clear recommendations on what FiO_{2} to use or what oxygen pressures in blood to aim for in burn patients. The optimal target to guide oxygen supplementation in nonburn critically ill patients also remains a subject of debate as large trials comparing liberal with conservative oxygen strategies in ventilated patients showed conflicting results [27–30]. Ventilatory data was collected at 08.00 am, provided that the patient was stable. As this was an observational study, no protocol to limit airway interventions before data collection was used. If such interventions were performed, they could have influenced the ventilatory data. For instance, V_{T} size could have been affected by the performance of suctioning, which may result in alveolar derecruitment [31], or by recruitment of collapsed alveoli though recruitment maneuvers [32]. Extrapolation of lung-protective ventilation strategies to the burn population is controversial as burn patients were generally excluded from benchmark ventilation studies [5,33–35]. Specific characteristics of burn patients may hamper applicability of lung-protective ventilation settings. Higher driving and plateau pressures may be required in patients with decreased pulmonary and chest wall compliance caused by circumferential abdominal and
thoracic burns. We did not collect data on the percentage of total body surface area with third degree burns nor on the presence of circumferential thoracic burns requiring thoracic escharotomy. Notably, eschar formation or pulmonary edema from the injury itself or from aggressive fluid resuscitation, can increase pulmonary problems [24,36].

Also, low VT ventilation can lead to ‘permissive hypercapnia’ [37]. Such hypercapnia may not be acceptable in burn patients who frequently require a high minute ventilation due to the markedly increased carbon dioxide production caused by the hypermetabolic response after a severe burn injury [36]. Higher VT may be required to improve oxygenation and ventilation in burn patients [24,38,39]. The only randomized controlled trial comparing a low VT strategy with high-frequency ventilation in adult burn patients was stopped prematurely after inclusion of 62 out of the 170 planned patients [38]. There were safety concerns as approximately one-third of the patients ventilated with low VT failed to meet oxygenation and ventilation goals [38]. Although low VT ventilation was applied in the majority of patients in our study, it remains uncertain whether burn patients benefit from this strategy. The lack of a relationship between VT and patient outcome was also reported in recent cohort studies in nonburn patients [21,40]. A randomized controlled trial comparing low with intermediate VT (i.e. 7 vs 9 mL/kg PBW) in nonburn ICU patients without ARDS also showed no significant difference in the number of VFD-28 or other clinical outcomes [41]. Future studies on ventilation strategies in burn patients could also target a driving pressure <15 cmH2O to investigate whether VT adjusted for respiratory compliance provides better outcomes.

In our study, ARDS occurred in ∼18% of patients, with no significant difference between patients with and without inhalation trauma. This is considerably higher when compared to nonburn patients [3,4]. In burn patients, the reported incidence of ARDS ranges widely [15,33,42]. Pneumonia occurred significantly more often in patients with inhalation trauma. Similar to prior studies, most cases were diagnosed within the first week post-burn [18,43]. Indeed, pneumonia is a common complication following inhalation injury and is considered an important risk factor for mortality in those patients [44].

The LAMiNAR results come with limitations. Given the lower than needed number of patients included, we simplified our analysis and focused on the impact of VT or presence of inhalation trauma on the number of VFD-28. Still, the results of this analysis should be regarded with caution as the study was underpowered. VFD-28 was used as the main clinical outcome parameter. This composite outcome parameter does not discriminate between mortality and ventilation duration of more than 28 days [45]. To account for this limitation, we performed a competing risk analysis and reported both components of our composite outcome [45].

We did not account for potential confounders such as the severity of burn injury, severity of inhalation trauma, applied nebulizer protocols, applied fluid strategy and use of sedatives and analgesics. Timely burn wound excision and grafting could impact mechanical ventilation as it improves chest wall compliance, limits the hypermetabolic response and potentially reduces the volumes required for fluid resuscitation [46–49]. As limited data on surgical aspects of burn care were collected, we did not account for surgical procedures as possible confounding factors. Although the large number of participating specialized burn centers increases generalizability, it also means that there were only a few patients per center. We analyzed pooled data to describe current ventilation practices and did not adjust for between-center differences [50]. Also, participation bias may have occurred, as burn centers with particular interest in ventilation practices could have been more prone to participate in LAMiNAR.

Conclusions
In this international cohort study we found that lung-protective ventilation is used in the majority of burn patients, irrespective of the presence of inhalation trauma. Use of low VT was not associated with a reduction in VFD-28. LAMiNAR provides relevant insights into current ventilation practices in burn patients, which could serve as a baseline in future randomized trials investigating MV strategies in burn patients.

Supplementary data
Supplementary material is available at Burns & Trauma journal online.

Abbreviations
ARDS: acute respiratory distress syndrome; FiO2: fraction of inspired oxygen; ICU: intensive care unit; IQR: interquartile range; IRB: institutional review board; LAMiNAR: Local Assessment of MaNagement in BuRN Patients; LIS: Lung injury scores; LOS: length of stay; MV: mechanical ventilation; PBW: predicted body weight; PEEP: positive end-expiratory pressure; Pmax: maximum airway pressure; Ppeak: peak airway pressure; Pplat: plateau pressure; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; VFD-28: ventilator-free days and alive at day 28; VILI: ventilator-induced lung injury; VT: tidal volume

Funding
Funded by ‘Nederlandse Brandwonden Stichting’ (the Dutch Burn Association, Beverwijk, The Netherlands).

Availability of data and material
De-identified individual participant data will be available on request from researchers, after approval of proposal by the steering committee. The data will be available by contacting the principal investigator after publication.
**Authors’ contributions**

Steering committee: concept and design of the study and writing of the study protocol. National coordinators and steering committee: recruitment of participating centers. National and local coordinators: ensured the study conducted conforms to good clinical practice. Local coordinators and collaborators: patient enrollment and data collection. ASN, JMB, GJG: statistical analysis. Writing committee: data interpretation and writing of the manuscript. Steering committee and national coordinators: critical revision of the manuscript for important intellectual content. MJS: principal investigator.

**Ethics approval**

The study protocol was centrally approved by the Institutional Review Board (IRB) of the Academic Medical Center at the University of Amsterdam, The Netherlands (W14_314#15.0178). All participating sites submitted the study protocol to their (local) IRB or regulatory authority and obtained ethical approval prior to initiation of the study, in compliance with the applicable local regulatory requirements.

**Consent for publication**

All authors approved the manuscript and this submission.

**Competing interests**

None declared.

**Acknowledgments**

We sincerely thank all participating investigators and patients.

**References**

1. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. JAMA. 2018;319:698–710.
2. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2014;370:980.
3. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 30 countries. JAMA. 2016;315:788–800.
4. Neto AS, Barbas CS, Simonis FD, Artigas-Raventos A, Canet J, Determann RM, et al. Epidemiological characteristics, practice of ventilation, and clinical outcome in patients at risk of acute respiratory distress syndrome in intensive care units from 16 countries (PRoVENT): an international, multicentre, prospective study. Lancet Respir Med. 2016;4:882–93.
5. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The acute respiratory distress syndrome network. N Engl J Med. 2000;342:1301–8.
6. Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P. Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann Intern Med. 2009;151:666–76.
7. Determann RM, Royakkers A, Wolthuis EK, Vlaar AP, Choi G, Paulus F, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Crit Care. 2010;14:R1.
8. Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Pasqualucci MO, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012;308:1651–9.
9. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;195:1253–63.
10. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580–637.
11. Esteban A, Ferguson ND, Meade MO, Frutos-Vivar F, Apezteguia C, Brochard I, et al. Evolution of mechanical ventilation in response to clinical research. Am J Respir Crit Care Med. 2008;177:170–7.
12. Steinval I, Bak Z, Sjoberg F. Acute respiratory distress syndrome is as important as inhalation injury for the development of respiratory dysfunction in major burns. Burns. 2008;34:441–51.
13. Mosier MJ, Pham TN. American burn association practice guidelines for prevention, diagnosis, and treatment of ventilator-associated pneumonia (VAP) in burn patients. Journal of burn care & research: official publication of the American Burn Association. 2009;30:910–28.
14. Badulak JH, Schurr M, Sauaia A, Ivashchenko A, Peltz E. Defining the criteria for intubation of the patient with thermal burns. Burns. 2018;44:531–8.
15. Glas GJ, Horn J, van der Hoeven SM, Hollmann MW, Clefken B, Colpaert K, et al. Changes in ventilator settings and ventilation-induced lung injury in burn patients—a systematic review. Burns. 2020;46(4):762–70.
16. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis. 1988;138:720–3.
17. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22:707–10.
18. Albright JM, Davis CS, Bird MD, Ramirez L, Kim H, Burnham EL, et al. The acute pulmonary inflammatory response to the graded severity of smoke inhalation injury. Crit Care Med. 2012;40:1113–21.
19. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the berlin definition. JAMA. 2012;307:2526–33.
20. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute kidney injury network: report of an
initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
21. Simonis FD, Barbos CSV, Artigas-Raventos A, Caner J, Dettmann RM, Anstey J, et al. Potentially modifiable respiratory variables contributing to outcome in ICU patients without ARDS: a secondary analysis of PROVENT. Ann Intensive Care. 2018;8:39.
22. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Vol. 1988, 2nd edn. Hillsdale,NJ: Lawrence Erlbaum, 1988, 2nd edition.
23. Scheike TH, Zhang MJ. Flexible competing risks regression modeling and goodness-of-fit. Lifetime Data Anal. 2008;14:464–83.
24. Chung KK, Rhie RY, Lundy JB, Cartotto R, Henderson E, Pressman MA, et al. A survey of mechanical ventilator practices across burn Centers in North America. Journal of burn care & research: official publication of the American Burn Association. 2016;37:e131–9.
25. Mekontso Dessap A, Boissier F, Charron C, Begot E, Repesse X, Legras A, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. Intensive Care Med. 2016;42:862–70.
26. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372:747–55.
27. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. JAMA. 2016;316:1583–9.
28. Chu DK, Kim LH, Young Pj, Zamiri N, Almenawer SA, Jaeschke R, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet (London, England). 2018;391:1693–705.
29. Barrot L, Asfar P, Mauny F, Winiszewski H, Montini F, Badie J, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med. 2020;382:999–1008.
30. Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, Eastwood G, et al. Conservative oxygen therapy during mechanical ventilation in the ICU. N Engl J Med. 2020;382:989–98.
31. Maggiore SM, Lellouche F, Pigeot J, Taille S, Deye N, Durrmeyer L, et al. Prevention of endotracheal suctioning-induced alveolar derecruitment in acute lung injury. Am J Respir Crit Care Med. 2003;167:1215–24.
32. Hartland BL, Newell TJ, Damico N. Alveolar recruitment maneuvers under general anesthesia: a systematic review of the literature. Respir Care. 2015;60:609–20.
33. Lundy JB, Chung KK, Pampin JC, Ainsworth CR, Jeng JC, Friedman BC. Update on severe burn Management for the Intensivist. J Intensive Care Med. 2016;31:499–510.
34. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008;299:646–53.
35. Brower RG, Lanken PN, Machntrye N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;351:327–36.
36. Bittner EA, Shank E, Woodson L, Martyn JA. Acute and perioperative care of the burn-injured patient. Anesthesiology. 2015;122:448–64.
37. Nin N, Muriel A, Peñuelas O, Brochard L, Lorente JA, Ferguson ND, et al. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. Intensive Care Med. 2017;43:200–8.
38. Chung KK, Wolf SE, Renz EM, Allan PF, Aden JK, Merrill GA, et al. High-frequency percussive ventilation and low tidal volume ventilation in burns: a randomized controlled trial. Crit Care Med. 2010;38:1970–7.
39. Sousse LE, Herndon DN, Andersen CR, Ali A, Benjamin NC, Granchi T, et al. High tidal volume decreases adult respiratory distress syndrome, atelectasis, and ventilator days compared with low tidal volume in pediatric burned patients with inhalation injury. J Am Coll Surg. 2015;220:570–8.
40. Lafyef JG, Bellani G, Pham T, Fan E, Madotto F, Bajwa EK, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNGSafe study. Intensive Care Med. 2016;42:1865–76.
41. Simonis FD, Serpa Neto A, Binnekade JM, Braber A, Bruin KCM, Dettmann RM, et al. Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS: a randomized clinical trial. JAMA. 2018;320:1872–80.
42. Cartotto R, Li Z, Hanna S, Sano P, Wood D, Chung K, et al. The acute respiratory distress syndrome (ARDS) in mechanically ventilated burn patients: an analysis of risk factors, clinical features, and outcomes using the berlin ARDS definition. Burns. 2016;42:1423–32.
43. Chen MC, Chen MH, Wen BS, Lee MH, Ma H. The impact of inhalation injury in patients with small and moderate burns. Burns. 2014;40:1481–6.
44. Walker PF, Buehner MF, Wood LA, Boyer NL, Driscoll IR, Lundy JB, et al. Diagnosis and management of inhalation injury: an updated review. Crit Care. 2015;19:351.
45. Yehya N, Harhay MO, Curley MAQ, Schoenfeld DA, Reeder RW. Re-appraisal of ventilator-free days in critical care research. Am J Respir Crit Care Med. 2019;200(7):828–36.
46. Barret JP, Herndon DN. Modulation of inflammatory and catabolic responses in severely burned children by early burn wound excision in the first 24 hours. Arch Surg. 2003;138:127–32.
47. Moussa A, Lo CH, Cleland H. Burn wound excision within 24 h: a 9-year review. Burns. 2021;47(6):1300–1307.
48. Williams FN, Herndon DN, Jeschke MG. The hypermetabolic response to burn injury and interventions to modify this response. Clin Plast Surg. 2009;36:583–96.
49. Greenwood JE. Advantages of immediate excision of burn eschar. Anaesthes Intensive Care. 2020;48:89–92.
50. Basagaña X, Pedersen M, Barrera-Gómez J, Gehring U, Giorgis-Allemand L, Hoek G, et al. Analysis of multicentre epidemiological studies: contrasting fixed or random effects modelling and meta-analysis. Int J Epidemiol. 2018;47:1343–54.