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Original Article
Risk factors for acute respiratory distress syndrome in severe burns: prospective cohort study

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Abstract: Introduction: Age and inhalation injury are important risk factors for acute respiratory distress syndrome (ARDS) in the burned patient; however, the impact of interventions such as mechanical ventilation, fluid balance (FB), and packed red blood cell transfusion remains unclear. The purpose of this study was to determine the incidence of moderate and severe ARDS and its risk factors among burn-related demographic variables and clinical interventions in mechanically ventilated burn patients. Risk factors for death within 28 days were also evaluated. Method: A prospective longitudinal study was carried out over a period of 30 months between July 2015 and December 2017. Patients older than 18 years, with a burn injury and under mechanical ventilation were included. The outcomes of interest were diagnosis of ARDS up to seven days after admission and death within 28 days. The proportional Cox regression risk model was used to obtain the hazard ratio for each independent variable. Results: The cases of 61 patients were analyzed. Thirty-seven (60.66%) of the patients developed ARDS. The groups of patients with or without ARDS did not present differences regarding age, sex, burned body surface, or prognostic scores. Factors independently related to the occurrence of ARDS were age (hazard ratio [HR] = 1.04; 95% confidence interval [CI] 1.02-1.06; $P < 0.001$), inhalation injury (HR = 2.50; 95% CI 1.25-5.02; $P = 0.01$), and static compliance (HR = 0.97; 95% CI 0.94-0.99; $P = 0.03$). Tidal volume, driving pressure, acute renal injury, and FB between days 1 and 7 were similar in both groups. Accumulated FBs of 48, 72, 96, and 168 hours were also similar. Mortality at 28 days was 40.98% (25 patients). ARDS (HR = 3.63, 95% CI 1.36 to 9.68; $P = 0.01$) and burned body surface area (HR = 1.03, 95% CI 1.02 to 1.05; $P < 0.001$) were associated with death in 28 days. Conclusion: ARDS was a frequent complication and a risk factor for death in patients under mechanical ventilation, with large burned areas. Age and inhalation injury were independent factors for ARDS. Current tidal volume, driving pressure, red blood cell transfusion, acute renal injury, and FB were not predictors of ARDS.

Keywords: Acute respiratory distress syndrome, burn, smoke inhalation injury, fluid balance, risk factor, mortality

Introduction

ARDS is an important respiratory complication in burn patients. In retrospective studies, the prevalence reported in mechanically ventilated patients ranged from 32.6% to 53.2%, applying the most recent Berlin definition [1], and 39.5% in a prospective study using the prior American-European Consensus Conference (AECC) definition [2]. Inhalation injury, pneumonia, frozen fresh plasma transfusion, and age are the independent risk factors cited in these studies [1, 3]. ARDS increases the duration of mechanical ventilation and the number of organ dysfunctions and consequently has a great impact on mortality.

Fluid creep [4, 5], defined as resuscitation above that recommended by the Parkland formula, has been related to abdominal compartment syndrome [6] and pulmonary complications [7]. A survey investigating international practice in early resuscitation found that the Parkland formula was employed by 69.3% of respondents; the preferred crystalloid solution was Ringer lactate (91.1%). Paradoxically, it was found that 55% of the interviewed individuals responded as having provided larger volumes than initially estimated, but 70% felt they had offered the right amount [8]. Cancio et al. [9] determined that total body surface area (TBSA) and weight were associated with the intensity of volume replacement in the initial hours. These authors detected incongruence between urinary output and Ringer's lactate infusion rate; in 11% of the patients with low diuresis, the rate of Ringer's lactate infusion was reduced, and 73.2% of patients with high urine output presented a maintained or increased infusion rate.

Pulmonary injury induced by mechanical ventilation may also be present in the burn patient. The International Society for Burn Injury recommends a protective ventilation strategy, although to date there are no studies demonstrating its benefit in this subpopulation of patients [10]. Transfusion of blood components also increases the risk of lung injury. Recently, Palmieri et al. demonstrated in a prospective randomized trial that a restrictive transfusion strategy reduced red blood cell usage, although there was no benefit regarding organ dysfunction and mortality [11]. Although great advances have been made in the clinical treatment of burn patients in recent years, gaps still exist. The purpose of this study was to evaluate the impact of characteristics of severely burned patients and clinical interventions, including mechanical ventilation, fluid balance, and packed red blood cell transfusion, the incidence of moderate and severe ARDS, and mortality within 28 days.

Materials and methods

Patients, location, inclusion and exclusion criteria, and ethical aspects

A prospective cohort study was performed, including all patients with burns admitted to the burn intensive care unit, older than or equal to 18 years, and who began invasive mechanical ventilatory support in the past 24 hours. The patients were admitted consecutively to the burn intensive care unit (BICU) of University Hospital of Londrina State University, between July 2015 and December 2017. Patients were excluded if they were diagnosed with ARDS at admission, had been in a hospital less than 24 hours, were readmitted to the unit, had been withdrawn from mechanical ventilation in less than 24 hours, or were admitted with a burn time greater than seven days. The primary outcome was the incidence of ARDS at seven days after BICU admission; the secondary outcome was survival at 28 days.

This research was submitted to and approved by the local Ethics Committee, under number CAAE 44807915.0.0000.5231. Written consent was requested from the legal representative of the eligible patients because their clinical conditions did not allow the information to be obtained directly.

Description of burn patient care

Patients are evaluated in the emergency room, and initial volume resuscitation and debridement of the lesions, as well as invasive procedures such as venous access, urinary catheter, and enteral catheter, are initiated when indicated. The body surface area (BSA) calculation is performed according to Lund and Browder [12] and defined by a plastic surgeon experienced in the care of burn patients. The calculation of fluid resuscitation volume is performed using the modified Brooke formula [13]. The decision regarding the need for intensive care is made by the plastic surgeon and intensivist care physician. Orotracheal intubation and mechanical ventilation are indicated in the presence or anticipation of inhalation injury with dyspnea. Inhalation heparin is used in patients who present with inhalation injury. Routinely, the initial ventilatory mode used is the volume cycle, and the tidal volume employed is calculated for each patient at 6 ml/kg of ideal weight.

Daily dressing changes are performed with the application of 1% silver sulfadiazine and the use of other dressings containing silver. If the patient can be transported to the operation room, dressing changes are performed under general anesthesia; otherwise, they occur in the BICU bed, under intravenous analgesia. Skin grafts are provided as soon as the clinical and hemodynamic stability is restored and the infection, if any, is under control.

The indication of red blood cell transfusion is at the discretion of intensive care physicians and plastic surgeons. In conditions in which there is no hemorrhagic shock, evaluations are performed daily and the trigger for transfusion is a hemoglobin dosage of less than 7 g/dl in patients who are stable hemodynamically and who do not have a scheduled surgical procedure. For those patients with a scheduled surgical procedure, the trigger for transfusion is 10 mg/dl of hemoglobin, performed the evening before the surgery. Following the procedure, a new measurement is performed six hours after readmission to the BICU.

Variables, definitions, and monitoring

Data was collected using patient records. At admission to the BICU, the following were noted: identification data; age and gender; weight, height, and body mass index (BMI); presence of chronic diseases; date of orotracheal intubation; date and diagnosis at hospital and BICU admission; TBSA; the presence of third degree burn areas; any accelerating agent associated with the burn; and environment in which the burn occurred. In the first 24 hours after admission to the BICU, clinical and laboratory data was collected to calculate the Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II) [14], Sequential Organ Failure Assessment (SOFA) [15], and Abbreviated Burn Severity Index (ABSI) [16]. The Kidney Disease Improving Global Outcomes (KDIGO) was used to define renal dysfunction [17]. The use of red blood cells and furosemide, tidal volume (ml), final positive expiratory pressure (PEEP, cmH_2O), total respiratory frequency (rpm), plateau pressure (cmH_2O), fraction of inspired oxygen (FiO_2, %), arterial pH, arterial oxygen partial pressure (PaO_2, mmHg), arterial partial pressure of carbon dioxide ($PaCO_2$, mmHg), and bicarbonate (HCO_3, mmHg) were measured daily for seven days. Dates of extubation and vital condition at 28 days were recorded.

The fluid balance was calculated by subtracting the outputs (urinary output, ultrafiltration volume during hemodialysis, other losses from drains and probes and free water loss from the burned area) from the infusions (intravenous infusions including parenteral nutritional support, blood products, enteral diet, fluids used for drug dilution). The insensible loss of water through the burn was calculated at 62 ml/m^2/hour of burned surface area [18]. To obtain the burned surface area, the body surface area (BSA) was calculated according to the Mosteller formula [19]. This value was then multiplied by the percentage of total burned body surface area (TBSA) in decimal numbers, which resulted in the surface area burned in m^2.

The diagnosis of inhalation injury was suspected in patients with a history of an accident indoors and a facial burn with scorched nasal vibrissae, carbonaceous expectoration, hoarseness, stridor, or dyspnea. Bronchoscopy was performed to confirm the presence of lesions in the lower airways in patients with suspected inhalation injury. For patients with inhalation injury, inhaled heparin was routinely used as adjunctive therapy.

Ventilation strategy adopted was low tidal volume ventilation for all patients using mechanical ventilation (6 ml/kg of predicted body weight). A volume-controlled mode was applied with constant inspiratory flow, and the PEEP level was selected from a PEEP-FiO_2 table as described previously [20]. Static compliance was measured during mechanical ventilation by activating a manual inspiratory pause and recording the compliance displayed by the ventilator. During static compliance measurement, no spontaneous breathing was allowed. Driving pressure was calculated as plateau pressure minus PEEP.

ARDS was defined and classified according to the Berlin criteria [21] within one week of thermal injury, considering it to be the insult associated with ARDS. The diagnosis of ARDS was made when acute onset of worsening oxygenation was observed by a PaO_2/FiO_2 ratio less than 300 mmHg sustained for at least 24 hours; PEEP settings of at least 5 cm H_2O; chest X-ray showing bilateral opacities interpreted by the attending physician; and volume overload and cardiogenic pulmonary edema were not mandatory to be ruled out, since there was a predisposing factor to ARDS in all cases considered to be the thermal injury. The daily notes of the patient's hospitalization period were reviewed by the first author (M. T. T.) to detect the diagnosis of ARDS up to the seventh day of hospitalization.

The dates of diagnosis of ARDS, as well as the beginning and end of mechanical ventilation, were also recorded. Patients were followed up until death, extubation, the time of diagnosis of ARDS, or the seventh day of hospitalization, whichever came first.

Statistical analysis

The results of the continuous variables are described as mean, standard deviation (SD), or median and interquartile (ITQ) range, depending on the distribution of the data. The Student's *t*-test was used to compare the means of the continuous variables with normal distribution and homogeneity of variances, and the Mann-Whitney U test was applied for data with non-normal distribution and/or heterogeneity of variances. Categorical variables were analyzed using the chi-square test and are presented as absolute and relative frequency. The cumulative incidence and time to onset of ARDS up to the seventh day and survival at 28 days in both groups were assessed by the Kaplan-Meier curve. The level of significance adopted was 5%.

The presence of associations between potential risk factors and dependent variables (ARDS in seven days and vital condition in 28 days) is presented as unadjusted hazard ratio (HR) and 95% confidence interval (95% CI), and was obtained through the proportional Cox risk regression model in Enter mode (bivariate analysis). For the multivariate analysis, the hierarchical Cox proportional hazards regression model was used. The 10 events per independent variable rule is considered the gold standard for the Cox regression model [22]; however, it is possible to use a rule of five to nine events per independent variable while maintaining acceptable levels of coverage and bias [23]. In this way, it was determined that the maximum number of variables for the two analyses would be six.

For the analysis of factors associated with ARDS in the Cox hierarchical regression model, the predictor variables were distributed into four hierarchies: (1) First hierarchy - variables at ICU admission: age, gender, TBSA, presence of third-degree burn, presence of inhalation injury, and etiology. (2) Second hierarchy - variables related to clinical interventions and acute renal outcome during the first week: use of vasopressor drug, packed red blood cell transfusion, acute kidney injury (AKI). (3) Third hierarchy - variables related to mechanical ventilation on the first day: tidal volume, driving pressure, static compliance. (4) Fourth hierarchy - variables related to the fluid balance: accumulated 24-hour and accumulated 48-hour fluid balances.

For the analysis of factors associated with death in 28 days, the variables were distributed into three hierarchies: (1) First hierarchy - variables at ICU admission: age, gender, TBSA, presence of third-degree burn, presence of inhalation injury, and etiology. (2) Second hierarchy - variables related to clinical interventions and outcomes during the first week: use of a vasopressor drug, packed red blood cell transfusion, acute kidney injury, and ARDS. (3) Third hierarchy - variables related to fluid balance: accumulated 24-hour and accumulated 48-hour fluid balances.

The variables ABSI, APACHE II, and SOFA on day 1 and mean dose of furosemide were withdrawn from the analysis due to the risk of collinearity with variables at ICU admission and renal dysfunction. The analysis was performed using the MedCalc program for Windows, version 18.2.1 (MedCalc Software, Mariakerke, Belgium).

Results

The flowchart in **Figure 1** demonstrates the number of patients screened and excluded; 61 patients remained in the analysis.

Thirty-seven patients (60.66%) presented with ARDS in the period of observation. The mean time for this diagnosis was 4.84 (SD: 2.6) days after the burn. Young and male patients were predominant. However, patients who did not develop ARDS were even younger (median age: 30 [ITQ: 24-42.5] versus 43 [ITQ: 32.75 to 59.5] years, P = 0.011). The burn characteristics were similar in both groups, but the frequency of inhalation injury was higher in patients with ARDS (7 [59.5%] versus 22 [29.2%], P = 0.022). The median ABSI score was higher in patients with ARDS (7; ITQ: 6-8) compared to patients without ARDS (6; ITQ: 5-7, P = 0.026) (**Table 1**).

There were no differences in clinical interventions between the comparison groups. Mortality in the ICU (7 [29.2%] versus 24 [64.9%], P = 0.007) at 28 days (5 [20.8%] versus 20 [54.1%], P = 0.011) and in-hospital mortality (8 [33.3%] versus 24 [64.9%], P = 0.017) was lower among patients without ARDS (**Table 2**).

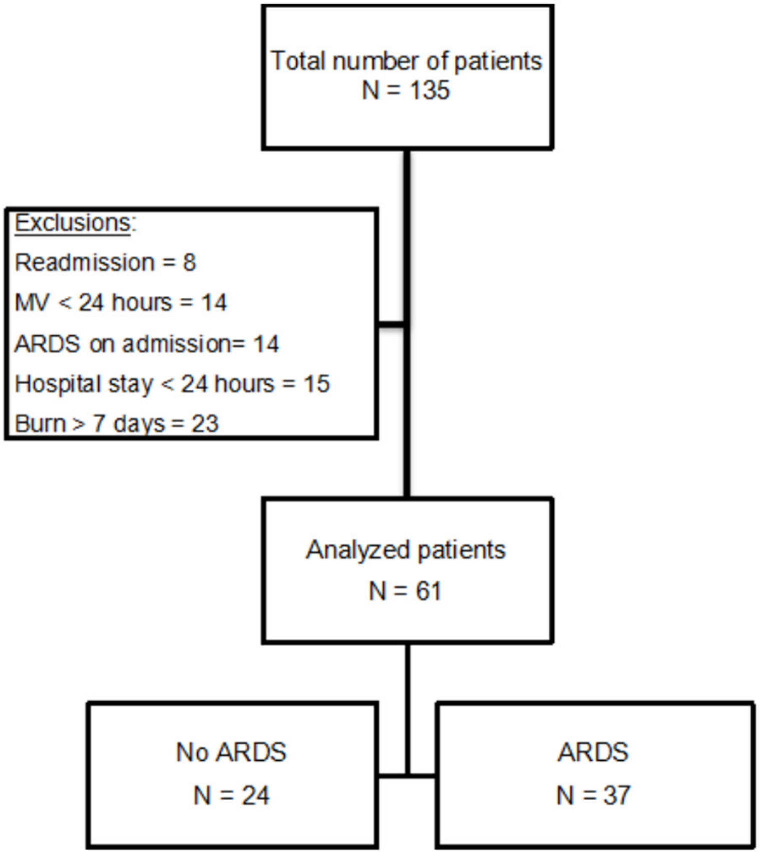

Figure 1. Study flowchart of patients. A total of 135 patients were screened to enter the study, 74 met exclusion criteria and 61 were analyzed. MV - mechanical ventilation; ARDS - acute respiratory distress syndrome.

Analyses of mechanical ventilation variables showed no difference between the groups. The tidal volume (**Figure 2A**), driving pressure (**Figure 2B**), and plateau pressure (**Figure 3**) observed between the first and seventh day of follow-up were similar between the two groups of patients and were prescribed following the recommendations for protective ventilation of the lungs. Median value of static compliance was lower in patients with ARDS during the first seven days of the study, although it did not reach statistical significance (**Figure 4**). The daily fluid balance between the first and seventh day (**Figure 2C**) and the accumulated fluid balance at 24, 48, 72, 96, and 168 hours of observation were no different between the groups (**Figure 2D**).

In the bivariate analysis, the hierarchy of variables at BICU admission showed that age (HR = 1.02, 95% CI 1.01-1.04, P = 0.009) and chemical burn (HR = 7.80, 95% 1.04-58.24, P = 0.045) were associated with evolution to ARDS. Burned body surface, presence of third-degree burn, and male gender were not associated with ARDS. Neither the accumulated fluid balance nor the ventilatory variables were associated with ARDS.

The final hierarchical Cox proportional hazards regression model showed that for each additional year of age the risk of ARDS increased by 4% (HR = 1.04, 95% CI 1.02-1.06, P < 0.001), the presence of inhalation injury increased the risk by 2.5 times (HR = 2.50, 95% CI 1.24-5.02, P = 0.010), and for each elevation of 1 ml/cm$H_2$0 in static compliance, the risk was reduced by 3% (HR = 0.97, 95% CI 0.94-0.99, P = 0.030) (**Table 3**).

The mean percentage of TBSA was higher in patients who did not survive 28 days compared to those who survived (23.82 [SD: 12.86] versus 40 [SD: 18.67], P < 0.001). Age, males, height, weight, BMI, presence of inhalation injury, third-degree burn, etiology, accelerating agent, and motive were no different between groups. The presence of vasopressor drugs at admission was higher in the group of non-surviving patients (18 [50%] versus 19 [76%], P = 0.042). Among the prognostic scores, ABSI median (6 [ITQ: 5-7] versus 8 [ITQ: 7-9], P < 0.001), and APACHE II mean (17.08 [SD: 7.27] versus 22, 28 [SD: 10.31], P = 0.024) were higher among patients who did not survive (**Table 4**).

The frequency of use and median dose of packed red blood cells, frequency of diuretic use, and AKI were similar between the two groups. The frequency of ARDS was higher among non-survivors (survivors 17 [47.2%] versus non-survivors 20 [80%], P = 0.011). The daily fluid balance between the first and seventh day of observation and the accumulated fluid balance at 24, 48, 72, 96, and 168 hours

Table 1. Characteristics of patients at ICU admission, according to the presence of ARDS

	All patients (n=61)	No ARDS (n=24)	ARDS (n=37)	P
Age (years)	39 [27-51.25]	30 [24-42.5]	43 [32.75-59.50]	0.011
Masculine sex (n,%)	43 (70.50)	19 (79.2)	24 (64.90)	0.234
Height (cm)	174 [164.75-177.50]	175.50 [169.5-182]	169 [163-176]	0.016
Ideal weight (kg)	67 [60-72.50]	71 [64.5-77]	64 [58.50-71]	0.014
Actual weight (kg)	75 [65-90]	80 [69-90]	75 [65-90]	0.716
Body mass index (kg/m^2)	25.71 [23.15-28.84]	24.67 [23.32 to 27.02]	26.26 [22.77-29.86]	0.240
BSA (m^2)	1.88 [1.77-2.08]	1.96 [1.80 to 2.09]	1.86 [1.75-2.07]	0.364
TBSA (%)	26 [17.75-41]	26.5 [20.25 to 40]	26 [16.87-43.37]	0.796
BBSA (m^2)	0.54 [0.34-0.84]	0.54 [0.37 to 0.75]	0.54 [0.31-0.88]	0.756
3rd degree burn (n, %)	14 (23)	4 (16.70)	10 (27)	0.351
Inhalation Injury (n, %)	29 (47.50)	7 (29.20)	22 (59.5)	0.022
Motive (n, %)				0.467
Work accident	13 (21.30)	6 (25)	7 (18.90)	
Domestic accident	35 (57.40)	13 (54.20)	22 (59.50)	
Homicide	6 (9.80)	1 (4.20)	5 (13.50)	
Suicide	7 (11.50)	4 (16.70)	3 (8.10)	
Etiology (n, %)				0.199
Electric	6 (9.80)	4 (16.70)	2 (5.40)	
Chemical	2 (3.30)	0 (0.00)	2 (5.40)	
Thermal	53 (86.90)	20 (83.30)	33 (89.20)	
Etiological agent (n, %)				0.678
Alcohol	28 (45.90)	12 (50)	16 (43.20)	
High voltage	4 (6.60)	2 (8.30)	2 (5.40)	
Voltaic arc	1 (1.60)	1 (4.20)	0 (0.00)	
Flame	3 (4.90)	0 (0.00)	3 (8.10)	
Gas	3 (4.90)	1 (4.20)	2 (5.40)	
Gasoline	5 (8.20)	3 (12.50)	2 (5.40)	
Fire	10 (16.40)	4 (16.70)	6 (16.20)	
Hot liquids	1 (1.60)	0 (0.00)	1 (2.70)	
Tar	1 (1.60)	0 (0.00)	1 (2.70)	
Lightening	1 (1.60)	1 (4.20)	0 (0.00)	
Caustic soda	1 (1.60)	0 (0.00)	1 (2.70)	
Spray	1 (1.60)	0 (0.00)	1 (2.70)	
Thinner	1 (1.60)	0 (0.00)	1 (2.70)	
Vapor	1 (1.60)	0 (0.00)	1 (2.70)	
Use of vasopressor at ICU admission (n, %)	37 (60.70)	14 (58.30)	23 (62.20)	0.767
PaO_2/FiO_2 ratio at ICU admission (mmHg)	242 [189.25-333.25]	301 [225-347]	221 [182.5-320]	0.125
ABSI	7 [5-8]	6 [5-7]	7 [6-8]	0.026
APACHE II	19 [12-26.25]	20 [10-25.50]	19 [12-28.25]	0.768
SOFA at ICU admission	7 [5-11]	7 [5-10]	8 [5-11]	0.935

Legend: UTI - intensive care unit; ARDS - acute respiratory distress syndrome; BSA - body surface area; TBSA - total burned body surface area; BBSA - burnt body surface area; FiO_2 - inspired fraction of oxygen; ABSI - abbreviated burn severity index; APACHE - Acute Physiology and Chronic Health Evaluation; SOFA - sequential organ failure assessment. The values of continuous variables with non-normal distribution are expressed as median [interquartile range], analyzed using the Mann-Whitney test. The values of the continuous variables of normal distribution are expressed as mean (standard deviation), analyzed with the t test. Categorical variables are expressed in number and percentage, analyzed with the Chi-square test.

were no different between survivors and non-survivors, except for the mean fluid balance on the second day (1927.82 [SD: 1512.56] versus 1016.15 [SD: 1999.60] liters, P = 0.047) (**Table 5**).

Only the TBSA (HR = 1.03, 95% CI 1.02-1.05, P < 0.001) and the presence of ARDS (HR = 3.63, 95% CI 1.36-9.68, P = 0.010) were independently associated with death at 28 days (**Table 6**).

Table 2. Clinical interventions in the ICU and outcomes, according to the presence of ARDS

	All patients (n=61)	No ARDS (n=24)	ARDS (n=37)	P
Mechanical ventilation (days)	15 [8-25]	15.50 [8.50-22.50]	15 [8-28.25]	0.590
Transfusion of packed red blood cells (n, %)	30 (49.20)	15 (62.50)	15 (40.50)	0.096
Median packed red blood cells (IU)	2 [1.5-2]	2 [1.5-20]	2 [1.25-2]	0.417
Furosemide (n, %)	50 (82)	19 (79.20)	31 (83.80)	0.649
Acute Kidney Injury (n, %)	35 (59.02)	11 (45.83)	25 (67.57)	0.092
Length of ICU stay (days)	16 [9.50-32]	16.5 [13-31]	16 [8-32]	0.451
Length of hospital stay (days)	21 [12.50-40.50]	33 [18-45.50]	19 (8-33)	0.019
Mortality in the ICU (n, %)	31 (50.80)	7 (29.20)	24 (64.90)	0.007
Mortality in 28 days (n, %)	25 (41)	5 (20.80)	20 (54.10)	0.011
Hospital mortality (n, %)	32 (52.50)	8 (33.30)	24 (64.90)	0.017

Legend: ICU - intensive care unit; ARDS - acute respiratory distress syndrome. The values of continuous variables with non-normal distribution are expressed as median [interquartile range], analyzed using the Mann-Whitney test. The values of the continuous variables of normal distribution are expressed as mean (standard deviation), analyzed with the t test. The categorical variables are expressed in number and percentage, analyzed with the Chi-square test.

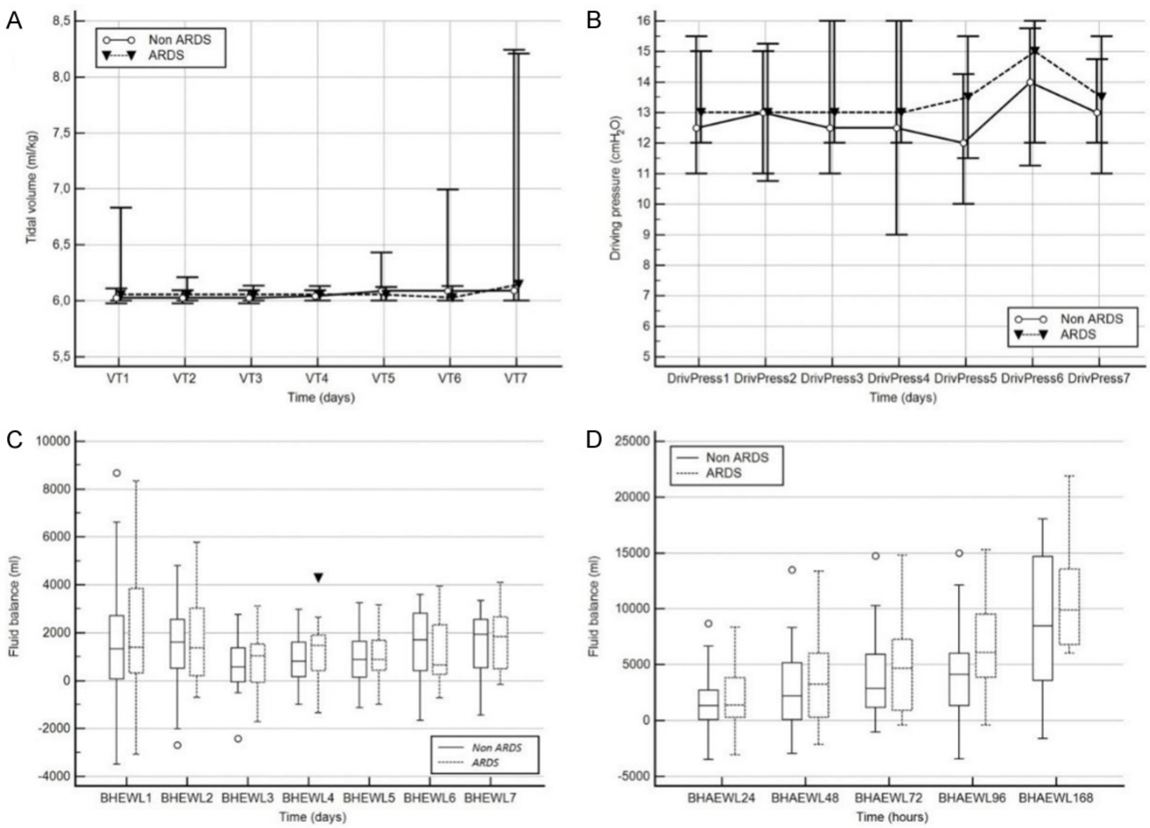

Figure 2. Mechanical ventilation variables and fluid balance according to the presence of ARDS during the first seven days of study. ARDS - acute respiratory distress syndrome; A. Daily tidal volume (median and interquartile ranges), according to the presence of ARDS. VT1 - tidal volume on study day 1; VT2 - tidal volume on study day 2; VT3 - tidal volume on study day 3; VT4 - tidal volume on study day 4; VT5 - tidal volume on study day 5; VT6 - tidal volume on study day 6; VT7 - tidal volume on study day 7. Value of $P > 0.05$ for all comparisons with day 1 (Mann-Whitney U test). B. Daily driving pressure (median and interquartile ranges), according to the presence of ARDS. DrivPress1 - driving pressure on study day 1; DrivPress2 - driving pressure on study day 2; DrivPress3 - driving pressure on study day 3; DrivPress4 - driving pressure on study day 4; DrivPress5 - driving pressure on study day 5; DrivPress6 - driving pressure on study day 6; DrivPress7 - driving pressure on study day 7. Value of $P > 0.05$ for all comparisons with day 1 (t-test). C. Daily fluid balance Box-and-Whisker, according to the presence of ARDS. BHEWL1 - fluid balance on study day 1; BHEWL2 - fluid balance on study day 2; BHEWL3 - fluid balance on study day 3; BHEWL4 - fluid balance on study day 4; BHEWL5 - fluid balance on study day 5; BHEWL6- fluid balance on

study day 6; BHEWL7 - fluid balance on study day 7. Value of $P > 0.05$ for all comparisons with day 1 (Mann-Whitney test). D. Accumulated fluid balance Box-and-Whisker, according to the presence of ARDS. BHAEWL24 - accumulated 24-hour fluid balance; BHAEWL48 - accumulated fluid balance of 48 hours; BHAEWL72 - accumulated fluid balance of 72 hours; BHAEWL96 - accumulated fluid balance of 96 hours; BHAEWL168 - accumulated fluid balance of 168 hours. *Value of $P < 0.05$ for the comparisons with day 1 in patients without ARDS (Mann-Whitney test). #Value of $P < 0.05$ for the comparisons with day 1 in ARDS patients.

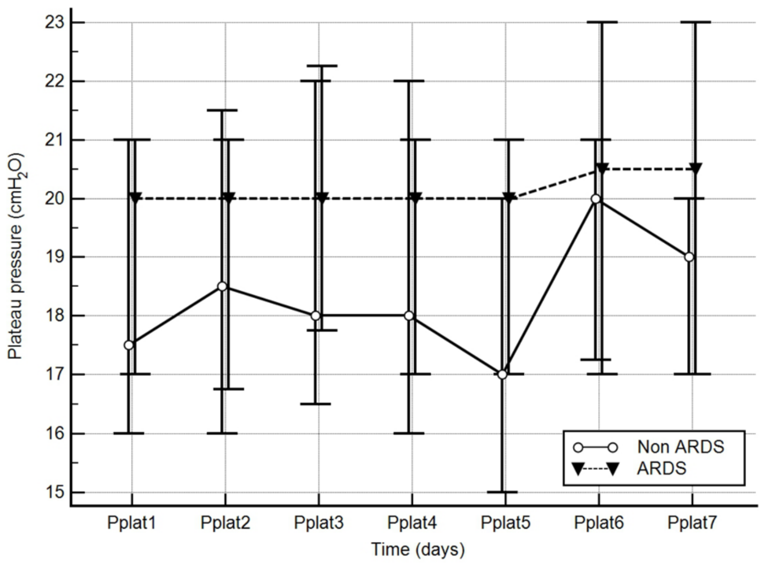

Figure 3. Plateau pressure according to the presence of ARDS during the first seven days of study. Plateau pressure is displayed as median and interquartile range. ARDS - acute respiratory distress syndrome; Pplat1 - plateau pressure on study day 1; Pplat2 - plateau pressure on study day 2; Ppla3 - plateau pressure on study day 3; Pplat4 - plateau pressure on study day 4; Pplat5 - plateau pressure on study day 5; Pplat6 - plateau pressure on study day 6; Pplat7 - plateau pressure on study day 7.

Discussion

We studied the effects of the predisposing and modifying factors related to burn patients, in addition to the clinical interventions that may potentiate the development of ARDS and its impact on mortality. The model of multiple inflammatory insults for the development of ARDS demonstrates the presence of a chain reaction among predisposing genetic factors, modifying factors (burn and inhalation injury), and a third factor represented by clinical interventions in these individuals, such as mechanical ventilation, blood transfusion, and fluid balance [24].

We found a high frequency of moderate and severe ARDS, as defined by Berlin definition [21], with a rapid evolution (mean time of 4.84 days). Dancey et al. [2] retrospectively analyzed 126 patients under mechanical ventilation (MV) and found a prevalence of 53.6% and time to diagnosis of 6.9 days, according to the American-European Consensus [25]. A more recent study retrospectively evaluated 891 patients and found a frequency of 28.7% of patients with moderate and severe ARDS, as defined by Berlin definition. In the comparison with the Am-|erican-European Consensus criteria, the Berlin definition stratified disease severity more adequately in more severe patients and excluded patients with minimal disease [26].

Age was a relevant factor for several clinical outcomes, including ARDS [2], due to frailty and lower organic reserve. In a comparative study between U.S. military and civilian patients, each additional year increased the probability of ARDS by 2% for civilian patients, who were on average 20 years older than military patients [27]. In the study by Sine et al., the mean age increased parallel to the severity, as defined by Berlin definition, and was an independently associated factor. With each additional year, the probability increased by 3% [26]. In the present study, patients with ARDS were older and with each year, the risk increased by 4%, consistent with other investigations.

In our study, the presence of inhalation injury increased the risk of ARDS. Although some investigators found an increased probability of ARDS in the presence of inhalation injury [27], other authors did not confirm this association [3, 26, 28]. The diagnostic definition of inhalation injury is still imprecise, since many authors advocate bronchoscopy and histopathological examination. In addition, there is no clear classification and stratification of the lesions [29]. The diversity of definitions for this

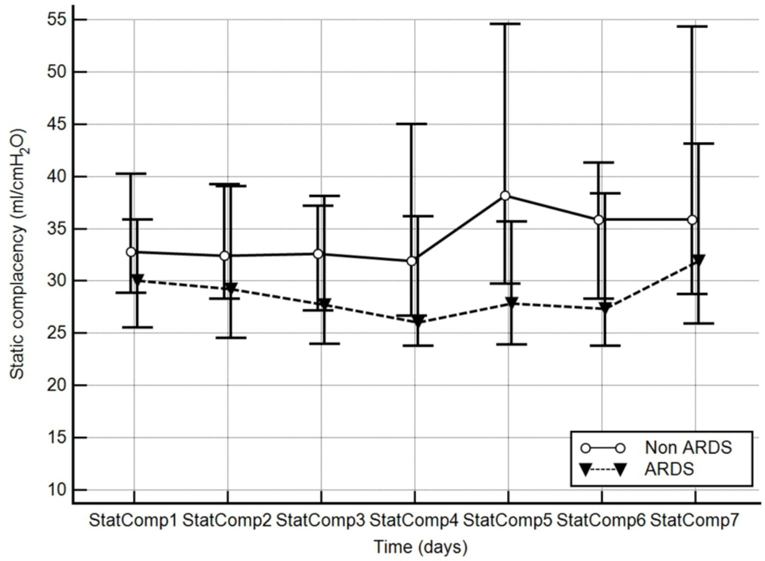

Figure 4. Static complacency according to the presence of ARDS during the first seven days of study. Static compliance is displayed as median and interquartile range. ARDS - acute respiratory distress syndrome; StatComp1 - static complacency on study day 1; StatComp2 - static complacency on study day 2; StatComp3 - static complacency on study day 3; StatComp4 - static complacency on study day 4; StatComp5 - static complacency on study day 5; StatComp6 - static complacency on study day 6; StatComp7 - static complacency on study day 7.

diagnosis may be one of the reasons for the disagreement in the results regarding the association between inhalation injury and ARDS [3, 29].

Although the Internatio nal Society for Burn Injury (ISBI) recognizes, in its recent Practice Guidelines [10], that the best ventilatory approach still remains to be defined, the institution supports that it is prudent to assume that lung injury associated with MV occurs in burn patients and recommends the use of protective ventilation. In the present study, tidal volume, plateau pressure, and driving pressure on the first day were similar in both groups and had no impact on the risk of ARDS. However, despite strictly following the recommendations of protective MV for all patients, the frequency of ARDS was high. Despite this, we believe that this strategy increases the safety in burned patients with inhalation injury. This rigorous practice was not verified by Chung et al. [30], who found wide variation in clinical practice in a survey conducted in 74 American specialized centers.

The static compliance on the first day was the only respiratory variable independently associated with the occurrence of ARDS. According to the Berlin definition [21], only bilateral radiological alteration, the presence of a risk factor up to seven days prior to diagnosis, and the PaO_2/FiO_2 ratio define ARDS. The reduction in static compliance is a pathological characteristic of the disease but does not represent a defining criterion. We then inquired whether there would be pulmonary injury, but no radiological or oxygenation representation, and whether the reduction in driving pressure would have an additional protective effect. Simonis et al. investigated the potential of low tidal volume (4 to 6 ml/kg) when compared to intermediate tidal volume (6 to 8 ml/kg) and found no differences in the incidence of ARDS, hospital mortality, or mechanical ventilator days [31]. A recent mechanistic study suggests that driving pressure showed a strong correlation with mortality risk, highlighting its potential usefulness in designing more protective ventilation strategies for this patient group [32].

Mechanical ventilation can be considered a second hit to the development of ARDS in trauma patients. Mechanical ventilation variables were not identified as risk factors for ARDS in our study, because all patients were ventilated homogeneously. In our sample, volume control mode was used in all patients, but there is recent evidence suggesting that early application of airway pressure release ventilation (APRV) could prevent the development of ARDS. Recent experimental evidence has suggested mechanisms by which APRV may reduce lung injury, including an improvement in alveolar recruitment and homogeneity; reduction in alveolar and alveolar duct micro-strain and stress-risers; reduction in alveolar tidal volumes; and recruitment of the chest wall by combating increased intra-abdominal pressure [33].

The effect of MV with positive pressure on fluid balance is well known. Increased intrathoracic

Table 3. Bivariate analysis and hierarchical Cox final regression model for independent factors for ARDS

	Bivariate analysis			*Cox final regression model*		
	Hazard ratio	Confidence interval 95%	P	*Hazard ratio*	Confidence interval 95%	P
1st Hierarchy - ICU admission variables						
Age	1.02	1.01-1.04	0.009	1.04	1.02-1.06	< 0.001
TBSA	1.00	0.98-1.02	0.996			
3rd degree burn	1.56	0.75-3.24	0.233			
Inhalation Injury	1.90	0.98-3.67	0.058	2.50	1.24-5.02	0.010
Masculine sex	1.27	0.65-2.49	0.490			
Chemical burn	7.80	1.04-58.24	0.045			
Thermal burn	1.94	0.46-8.08	0.364			
2nd Hierarchy - Interventions and outcome						
Vasopressor drug	1.16	0.60-2.26	0.660			
Red blood cell concentrate	0.47	0.24-0.92	0.027			
AKI	1.61	0.81-3.21	0.176			
3rd Hierarchy - Accumulated fluid balance						
Accumulated 24 hours	1.00	0.99-1	0.965			
Accumulated 48 hours	1.00	0.99-1	0.685			
4th Hierarchy - Ventilatory variables						
Current volume day 1	1.03	0.87-1.22	0.718			
Static compliance day 1	0.99	0.96-1.01	0.324	0.97	0.94-0.99	0.030
Driving pressure day 1	1.03	0.94-1.13	0.501			

Legend 1: ARDS - acute respiratory distress syndrome; ICU - intensive care unit; TBSA - total burned body surface area; AKI - acute kidney injury.

pressure causes a reduction in venous return and a consequent reduction in cardiac output. The low rate of glomerular filtration and increased renin activity reduce urine output, which can be interpreted as a suggestion for intensification of fluid resuscitation [34]. Mackie et al. [34] retrospectively evaluated 186 patients with or without inhalation injury and with or without MV, and the primary outcome was accumulated fluid balance. Patients mechanically ventilated, regardless of the presence of inhalation injury, presented accumulated fluid balance on days 3 and 7 of approximately 23 and 34 liters, respectively, against 13 liters of patients without MV. The mean accumulated fluid balance on days 3 and 7 in our sample was lower than that reported by Mackie et al., with 4.3 and 9.4 liters, respectively, and neither daily nor cumulative fluid balance was associated with ARDS.

Hospital mortality was high in our patients compared with survival predicted by the ABSI [16]. It should be considered that the ABSI is a score developed to evaluate a burn center integrally, including patients not in the BICU. In the present study, only those patients admitted to the BICU and on mechanical ventilation were included-that is, a population different from the one used for validation of the score. In addition, the mortality predicted by the ABSI may not be calibrated for countries with limited resources due to differences in clinical practice. Non-survivors were more severely burned, according to ABSI and APACHE II scores, with more frequent use of vasopressors. The frequency of furosemide use was similar in both groups, but the dose given to non-surviving patients was higher, which may explain the similarity in accumulated fluid balance in both groups, without increasing the frequency of AKI.

In our sample, we observed a 3% increase in the risk of death for each TBSA percentage point and 3.63 times in the presence of ARDS. Belenkiy et al. [1] found an increase in the probability of death on the order of 4.42 and 9.52 times for moderate and severe ARDS, respec-

Table 4. Characteristics of patients at ICU admission, according to 28-day survival

	Survivors (n=36)	Non survivors (n=25)	P
Age (years)	37 [24.5-47.5]	43 [30-56.5]	0.125
Male (n, %)	25 (69.40)	18 (72)	0.831
Height (cm)	171.42 (9.72)	171.96 (9.55)	0.830
Ideal Weight (kg)	65.86 (10.31)	66.4 (9.5)	0.836
Actual weight (kg)	74 [65-87.5]	80 [70-90]	0.397
Body mass index (kg/m^2)	24.78 [22.79-27.43]	26.35 [24.38-29.22]	0.241
BSA (m^2)	1.89 (0.20)	1.96 (0.28)	0.298
BBA (%)	23.82 (12.86)	40 (18.67)	< 0.001
BBSA (m^2)	0.46 (0.26)	0.79 (0.37)	< 0.001
3rd degree burn (n, %)	6 (16.7)	8 (32)	0.165
Inhalation Injury (n, %)	18 (50)	11 (44)	0.647
Etiology (n, %)			0.216
Electric	4 (11.1)	2 (8)	
Chemical	0 (0)	2 (8)	
Thermal	32 (88.9)	21 (84)	
Etiological agent (n, %)			0.282
Alcohol	16 (44.4)	12 (48)	
High voltage	2 (5.6)	2 (8)	
Voltaic arc	1 (2.8)	0 (0)	
Flame	3 (8.3)	0 (0)	
Gas	2 (5.6)	1 (4)	
Gasoline	5 (13.9)	0 (0)	
Fire	5 (13.9)	5 (20)	
Hot liquids	0 (0)	1 (4)	
Tar	0 (0)	1 (4)	
Lightening	1 (2.8)	0 (0)	
Caustic soda	0 (0)	1 (4)	
Spray	0 (0)	1 (4)	
Thinner	1 (2.8)	0 (0)	
Vapor	0 (0)	1 (4)	
Motive (n, %)			0.497
Work accident	6 (16.7)	7 (28)	
Domestic accident	21 (58.3)	14 (56)	
Homicide	5 (13.9)	1 (4)	
Suicide	4 (11.1)	3 (12)	
Vasopressor at ICU admission (n, %)	18 (50)	19 (76)	0.042
PaO_2/FiO_2 at ICU admission (mmHg)	282.11 (115.68)	251.28 (102.45)	0.288
ABSI	6 [5-7]	8 [7-9]	< 0.001
APACHE II	17.08 (7.27)	22.28 (10.31)	0.024
SOFA at ICU admission	6.83 (3.05)	8.4 (3.28)	0.060

Legend: UTI - intensive care unit; ARDS - acute respiratory distress syndrome; BSA - body surface area; BBS - burned body surface; BBSA - burnt body surface area; FiO_2 - inspired fraction of oxygen; ABSI - abbreviated burn severity index; APACHE - Acute Physiology and Chronic Health Evaluation; SOFA - sequential organ failure assessment. The values of continuous variables with non-normal distribution are expressed as median [interquartile range], analyzed using the Mann-Whitney test. The values of the continuous variables of normal distribution are expressed as mean (standard deviation), analyzed with the t test. Categorical variables are expressed in number and percentage, analyzed with the Chi-square test.

tively, and TBSA and age were also relevant for this outcome. Campos et al. [35] evaluated 163 burn patients and reported that TBSA, suicide attempts, and accumulated fluid balance were

Table 5. Clinical interventions in the ICU and outcomes, according to survival

	Survivors (n=36)	Non survivors (n=25)	P
Mechanical ventilation (days)	21 [11-28]	11 [6.75-16.25]	0.003
Transfusion of packed red blood cells (n, %)	20 (55,6)	10 (40)	0.236
Median packed red blood cells (UI)	2 [1-2]	2 [1.67-2]	0.229
Furosemide (n, %)	28 (77.8)	22 (88)	0.311
Median dose of furosemide (mg)	7.57 [2.67-23.09]	20 [8-45.95]	0.018
ARDS (n, %)	17 (47.2)	20 (80)	0.011
AKI (n, %)	20 (55.6)	16 (64)	0.513
Length of hospital stay (days)	36 [28-49]	11 [6.75-16]	< 0.001
Length of ICU stay (days)	28 [14.5-38]	11 [6.75-16]	< 0.001

Legend: ARDS - acute respiratory distress syndrome; AKI - acute kidney injury; ICU - intensive care unit.

Table 6. Bivariate analysis and hierarchical Cox final regression model for independent factors for death in 28 days

	Bivariate analysis			*Cox final regression model*		
	Hazard ratio	Confidence interval 95%	P	*Hazard ratio*	Confidence interval 95%	P
1st Hierarchy - ICU admission variables						
Age	1.02	0.99-1.04	0.102			
TBSA	1.03	1.01-1.05	0.001	1.03	1.02-1.05	< 0.001
Inhalation Injury	0.89	0.41-1.97	0.782			
3rd degree burn	1.71	0.74-3.97	0.210			
Masculine sex	0.90	0.38-2.16	0.819			
2nd Hierarchy - Interventions and outcome						
Vasopressor drug	2.32	0.93-5.82	0.072			
Red blood cell concentrate	0.53	0.24-1.18	0.119			
ARDS	3.39	1.27-9.05	0.015	3.63	1.36-9.68	0.010
AKI	1.25	0.55-2.84	0.587			
3rd Hierarchy - Accumulated fluid balance						
Accumulated 24 hours	1.00	1.00-1.00	0.096			
Accumulated 48 hours	1.00	0.99-1.00	0.812			

Legend: ICU - intensive care unit; TBSA - total burned body surface area; ARDS - acute respiratory distress syndrome; AKI - acute kidney injury.

independently associated with death. ARDS was not investigated by the investigators, but the median PaO_2/FiO_2 ratio was 160 mmHg (ITQ: 92-219) in non-survivors compared to 289 mmHg (ITQ: 211-340) in survivors, indicating respiratory organ dysfunction.

We considered the prospective design, absence of patient data loss, and search for major risk factors that affected burn-related ARDS, including clinical interventions over seven days of admission as strengths in our study. These interventions were the use of diuretics and the frequency of AKI, the use and dose of packed red blood cells, respiratory mechanics variables and their behavior, and fluid balance, which included an alternative way of estimating burn fluid losses, as indicated in the recent literature [18]. On the other hand, our small sample had limitations such as low statistical power and estimation of increased effect size and external validity due to the single-center model.

Conclusion

In this population of critically burned patients, with TBSA greater than 20%, or inhalation injury and mechanical ventilation, the incidence of moderate and severe ARDS was high. For each additional year of age, the risk for ARDS increased by 4%, and the presence of inhalation injury increased the risk by 2.5 times. No clinical intervention investigated in the present study was related to the risk of ARDS, and fluid balance and ventilatory variables were similar in both groups of patients. In addition to ARDS, TBSA was also a risk factor for death.

Disclosure of conflict of interest

None.

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