

Incidence and prognosis of intra-abdominal hypertension and abdominal compartment syndrome in severely burned patients: Pilot study and review of the literature

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Abstract

Background: Burn patients are at high risk for secondary intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) due to capillary leak and large volume fluid resuscitation.

Our objective was to examine the incidence the incidence of IAH and ACS and their relation to outcome in mechanically ventilated (MV) burn patients.

Methods: This observational study included all MV burn patients admitted between April 2007 and December 2009. Various physiological parameters, intra-abdominal pressure (IAP) measurements and severity scoring indices were recorded on admission and/or each day in ICU. Transpulmonary thermodilution parameters were also obtained in 23 patients. The mean and maximum IAP during admission was calculated. The primary endpoint was ICU (burn unit) mortality.

Results: Fifty-six patients were included. The average Simplified Acute Physiology Score (SAPS II) and Sequential Organ Failure Assessment (SOFA) scores were 43.4 (\pm 15.1) and 6.4 (\pm 3.4), respectively. The average total body surface area (TBSA) affected by burns was 24.9% (\pm 24.9), with 33 patients suffering inhalational injuries. Forty-four (78.6%) patients developed IAH and 16 (28.6%) suffered ACS. Patients with ACS had higher TBSAs burned (35.8 \pm 30 vs. 20.6 \pm 21.4%, P=0.04) and higher cumulative fluid balances after 48 hours (13.6 \pm 16L vs. 7.6 \pm 4.1L, *P* = 0.03). The TBSA burned correlated well with the mean IAP (*R* = 0.34, *P* = 0.01). Mortality was notably high (26.8%) and significantly higher in patients with IAH (34.1%, *P* = 0.014) and ACS (62.5%, *P* < 0.0001). Most patients received more fluids than calculated by the Parkland Consensus Formula while, interestingly, non-survivors received less. However, when patients with pure inhalation injury were excluded there were no differences. Non-surgical interventions (n = 24) were successful in removing body fluids and were related to a significant decrease in IAP, central venous pressure (CVP) and an improvement in oxygenation and urine output. Non-resolution of IAH was associated with a significantly worse outcome (*P* < 0.0001).

Conclusion: Based on our preliminary results we conclude that IAH and ACS have a relatively high incidence in MV burn patients compared to other groups of critically ill patients. The percentage of TBSA burned correlates with the mean IAP. The combination of high CLI, positive (daily and cumulative) fluid balance, high IAP, high EVLWI and low APP suggest a poor outcome. Non-surgical interventions appear to improve end-organ function. Non-resolution of IAH is related to a worse outcome.

Key words: abdominal pressure, abdominal hypertension, abdominal compartment syndrome, burns, incidence, fluid resuscitation, monitoring, treatment

Anaesthesiology Intensive Therapy 2015 [ahead of print]

Burn patients are at high risk of secondary intraabdominal hypertension (IAH) and abdominal compartment syndrome (ACS) due to capillary leak and large volume fluid resuscitation [1–3]. According to the recently revised consensus definitions of the World Society on Abdominal Compartment Syndrome (WSACS, www.wsacs.org), secondary ACS is defined as a sustained increase in intra-abdominal pressure (IAP) above 20 mm Hg with new onset organ dysfunction that does not originate from the abdominal-pelvic region [4, 5]. Secondary ACS is a common, and relatively under recognized, rapidly fatal condition in severely burned patients. The reported incidence varies from 30% to 80% [6]. The pathophysiological implications of IAH are numerous and can lead to acute renal failure, respiratory failure and splanchnic ischemia [7]. In addition, the physiological mayhem that ensues following a burn injury further complicates management. Urine output, often used as a marker of success in fluid resuscitation, may become an inadequate indicator during fluid management due to rising IAP, thus leading to overzealous administration and a large cumulative fluid balance. This will contribute to the development of secondary ACS. In previous studies, it was shown that peak inspiratory pressure correlates strongly with the IAP in patients with ACS [8]. However, with the advent of lung protective ventilation, these peak pressures are seldom seen. In contrast, a diminished chest wall compliance resulting in low tidal volumes and hypercapnia has become the hallmark of respiratory failure related to IAH and ACS [9].

While IAH may usually respond to conservative medical management (Table 1), surgical intervention with abdominal decompression is the only definitive treatment for ACS [10]. Although decompressive laparotomy aims to reverse worsening cardiovascular, respiratory and renal function, mortality remains high at 50%, despite this intervention [11]. A significant physiological improvement can, however, result following decompressive laparotomy, as reported by Hershberger *et al.*, where mean urine output improved from

 Table 1. Suggested medical interventions in burns patients suggested

 by the World Society on Abdominal Compartment Syndrome (WSACS)

 in the management of intra-abdominal hypertension [5]

Medical strategies in the management of intra-abdominal hypertension in burns

Improvement of abdominal wall compliance (sedation and paralysis, escharotomies, avoiding positive fluid balance)

Evacuation of intra-abdominal contents (percutaneous ascites drainage)

Evacuation of intraluminal contents (gastroprokinetics, stool softeners, enemas, adaptation of enteral nutrition speed)

Correction of capillary leak and fluid balance (hypertonic solutions, albumin 20%, colloids, diuretics, ultrafiltration)

Optimisation of organ perfusion

28 mL h⁻¹ to 90 mL h⁻¹ [12]. Latenser *et al.* demonstrated that percutaneous drainage in burn patients is a safe and effective alternative to decompressive laparotomy when patients have less than 80% TBSA involved [3].

Of particular interest is the choice of fluids used to resuscitate burn patients. Colloid resuscitation has not shown improved outcomes [13]. Plasma-resuscitated patients maintained an IAP below the threshold associated with frequent complications, and urine output and kidney function remained unchanged [14]. Oda et al. demonstrated that in patients with severe burn injuries, hypertonic lactated saline resuscitation could reduce the risk of secondary ACS [2]. Further comparisons evaluating the difference in survival between crystalloid resuscitation and lower infusion volume regimens have not yet been conducted. In line with the results of recent large fluid trials, the use of starches can no longer be recommended in burn patients, as was summarized in a concise review [15]. Although goal-directed treatment has been advocated in septic patients in the past [16], recent data from the ProCESS study could not confirm this and, as such, this cannot be recommended in burn patients [17]. This is supported by previous reports showing that volumetric monitoring may lead to even higher resuscitation volumes and possible adverse effects [18].

The aim of this study was to examine the incidence of IAH and ACS in severely burned patients under mechanical ventilation (MV) and to study prognostic factors. Furthermore, we wanted to analyse the effects of medical management on IAH and how non-resolution of IAH may have an impact on outcome. Finally, we attempted to establish a control group before changing our fluid resuscitation from the classic Parkland formula to a more restricted regimen with balanced crystalloids and colloids.

METHODS

ETHICS

The study was conducted in accordance with the ICU protocol, the declaration of Helsinki and applicable regulatory requirements as approved by the institutional review board and the local institutional ethics committee (approval number 3852). In view of the nature of the study being purely observational and not demanding a deviation from standard clinical ICU care, informed consent from the patient or the next of kin was not deemed necessary. Retrospective data analysis of existing information based on the standard of care did not, therefore, influence management. Medical records were secure and only accessed by treating ICU physicians. All data were anonymized prior to the analysis.

STUDY POPULATION

All consecutive patients requiring mechanical ventilation (MV) that were admitted to our burns unit between April 2007 and December 2009 (32 months) were considered in the analysis. Inclusion criteria included the presence of an isolated inhalation injury for which MV was necessary, or patients with > 20% total body surface area (TBSA) burn area in adults, or >15% TBSA burns in children with or without inhalation that received fluid resuscitation. Patients were excluded if there was an "allow natural death order", or an inability to measure IAP via the bladder or stomach. Fifty-six patients were included.

DATA COLLECTION

PATIENT DEMOGRAPHICS

Data collected on admission included the patients' age. gender, weight, height, body mass index, body surface area, and their date of enrolment. The origin of burns was recorded: flame, scald, or toxic, together with the presence of an inhalation injury, if applicable. The percentage of TBSA that was burned was recorded together with the presence of full thickness burns (3rd degree) and/or deep and superficial 2nd degree burns (all expressed as a %). Information pertaining to clinical and physiological parameters was recorded from admission to hospital discharge, death, or for a maximum of 28 days. This was done irrespective of whether they remained in the burn unit, or were transferred to another ward within the department (within the same hospital). Patients that were discharged to another hospital during the study were not followed after this transfer, but if possible a 28-day outcome was recorded. Secondary endpoints were the duration of ICU and hospital stay, and the use of resources: duration of MV, hemodynamic monitoring and renal replacement therapy (RRT).

SEVERITY SCORES

Several measurements were made pertaining to severity scoring, fluids administered, IAP, and transpulmonary thermodilution techniques. During the first 24 hours of admission to the burn unit, acute physiology and chronic health evaluation (APACHE II) and simplified acute physiology score (SAPS II) scores were calculated. Daily sequential organ failure assessment (SOFA) scores were recorded for the duration of the admission. For each patient the worst value for each organ system (respiratory, cardiovascular, renal, coagulation, liver and neurologic) in each 24-hour period was considered.

FLUID BALANCE

Although the daily fluid balance was recorded by subtracting the total losses from the total daily intake, insensible losses were not included in these calculations. Daily fluid intake was expressed as mL kg⁻¹ %TBSA and as mL kg⁻¹. Cumulative intake at 48 hours (end of resuscitation period) was calculated. Daily enteral nutrition intake was recorded. Urine output was expressed as millilitres per day and as mL kg⁻¹h⁻¹. When available, losses from nasogastric and percutaneous abdominal drains were noted. The cumulative fluid balance within the first 7 days of stay was calculated. The capillary leak index (CLI) was also calculated as a ratio, defined as the serum C-reactive protein (CRP (mg dL⁻¹)) divided by the serum albumin (g L⁻¹) levels.

IAP MEASUREMENT

IAP measurements were made with the Foley Manometer (Holtech Medical, Charlottenlund, Denmark) via a Foley bladder catheter. This measurement followed a standardized protocol in the unit as published before [19], and was measured in a stable, supine position, at least four times a day with the zero reference at the level where the mid-axillary line crosses the iliac crest [5]. Patients identified as having a sustained IAP \geq 12 mm Hg were monitored continuously via a balloon-tipped nasogastric probe connected to the Ci-MON monitor (Pulsion Medical Systems, Munich, Germany). Using the above techniques, daily records of the lowest (IAP_{low}) and highest (IAP_{high}) intra-abdominal pressure, and the lowest abdominal perfusion pressure (APP) were made. Abdominal perfusion pressure (APP) was defined as the mean arterial pressure (MAP) minus the corresponding IAP. The mean IAP (IAP $_{mean}$) and maximal IAP (IAP $_{max}$) were also calculated from the daily measurements during the first week of admission.

DEFINITIONS

According to the revised WSACS consensus definitions, IAH was defined as a sustained IAP equal to or higher than 12 mm Hg, while ACS was defined as a sustained IAP higher than 20 mm Hg with at least one new organ failure (as defined by a SOFA sub-score above 3) [5].

HEMODYNAMIC MONITORING

A central venous catheter was inserted in all the patients and a thermistor-tipped arterial thermodilution catheter (Pulsiocath 5F) was placed in the femoral artery in 23 patients. This was attached to a PiCCOplus or PiCCO₂ monitoring system (Pulsion Medical Systems, Munich, Germany). Transpulmonary thermodilution measurements were obtained by injection of three 20 mL boluses of cooled saline (< 8°C) into the central venous catheter. For each set of thermodilution determinants, the mean value was used for statistical analysis [20]. Cardiac output (CO), global end diastolic volume (GEDV), extravascular lung water (EVLW), global ejection fraction (GEF), pulmonary vascular permeability index (PVPI), stroke volume variation (SVV) and pulse pressure variation (PPV) were calculated. Further calculations were made by correlating EVLW to predicted body weight (EVLWI), and CO and GEDV to body surface area (CI, GEDVI).

STATISTICAL ANALYSIS

Only the data obtained during the first week, or less if discharge or death occurred before day 7, were used for statistical purposes. Continuous variables are presented as the mean (± standard deviation, SD) or median in the case of skewed distribution. Categorical variables are expressed as numbers and percentages for the group from which they were derived. Continuous variables were compared with the Student's t-test for normally distributed variables and the Mann Whitney test for non-normally distributed variables. The $\chi 2$ test or Fisher's exact test were used to compare ordinal variables. All p-values are two-tailed and a P value lower than 0.05 was considered statistically significant. Statistical analysis was done with SPSS (Windows version 16.0, Chicago, IL, USA). The primary endpoint of the population studied was mortality. Secondary endpoints included the incidence of IAH and ACS, and the prognostic value of non-resolution of IAH after medical management together with the use of ICU resources (MV, hemodynamic monitoring, RRT).

FLUID RESUSCITATION AND STANDARD TREATMENT

Over the first 24-48 hours, the burn patients were resuscitated according to the Consensus Formula as suggested by Parkland. A balanced crystalloid (Plasmalyte) at 4 mL kg⁻¹%TBSA burned was administered, together with a maintenance fluid of glucose 5% in 0.45% NaCl at 84 mL h⁻¹. Urine output was used to help titrate the volume of fluid resuscitation, with a goal directed urine output between 0.5 and 1.0 mL kg⁻¹h⁻¹. Enteral nutrition, following a unit specific standard protocol, was commenced from day 2 at 10 mL h⁻¹ and gradually increased. Colloids were allowed from day 2 and included mainly hyperoncotic albumin 20% (if serum levels were < 25 g L⁻¹) or balanced starches (Volulyte®, Fresenius-Kabi, Melsungen, Germany). Standard patient care was carried out in all individuals according to the protocols of the burn unit. Medical management for increased IAP was instituted to alleviate this problem (see Table 1) [21]. Abdominal decompression by laparotomy was used as the definitive treatment of ACS if the medical management implemented had failed to decrease the IAP.

RESULTS

PATIENT DEMOGRAPHICS

Table 2 summarizes the patient demographics and severity data for the whole group and in survivors vs. nonsurvivors. Fifty-six patients were included in the study, with an average age of 43.1 (\pm 25.9) years, mean weight of 68.5 (\pm 28.3) kg, and a BMI of 24.5 (\pm 6.3). Data pertaining to demographics and biometric measurements are shown in Table 2. The male to female ratio was 2: 1 and 10 children were included. The majority (n = 42) typically suffered flame burns, with a relatively high number (n = 33) also incurring inhalational injuries, while scald (n = 9) and toxic burns (n = 5) occurred less frequently.

SEVERITY SCORES

The average SOFA score was 6.4 ± 3.5 , with a trend towards a higher score in non-survivors (7.8 ± 4 vs. 5.9 ± 3.1 and a p-value of 0.062). The organ systems SOFA subscores which differed most between survivors and non-survivors were the cardiovascular (1.4 ± 1.2 vs. 2.4 ± 1.5 with p=0.015), and the liver subscores (0.2 ± 0.5 vs. 0.7 ± 0.8 with P = 0.013). Figure 1 (Panel A) represents the divergence of SOFA scores from day 2 in the non-survivor group. The SAPS scores were significantly higher in non-survivors (55.6 ± 15.1 vs. $39 \pm$ 12.5 with P < 0.0001).

MORTALITY AND OUTCOME PREDICTORS

The mortality rate was high at 26.8% (n = 15) and significantly higher in patients with IAH (34.1%, P = 0.014) and ACS (62.5%, P < 0.0001). In univariate analysis SAPS II, APACHE II, the TBSA burned, percentage of full-thickness third degree burns, IAP (low, high, mean and max), CLI, EVLWI (mean and max), PEEP, $P_{plat'}$ total fluid intake, daily and cumulative fluid balance were all significantly higher in non-survivors, while APP and albumin were significantly lower (Table 3). In parallel to the severity scoring, albumin was noted to be significantly lower in the non-survivors, with a divergence from the survivor group occurring on day 2, possibly also demonstrating the severity of their injuries (Fig. 1, Panel B).

On day 3 post injury, non-survivors were shown to have a higher capillary leak index, which once again may reflect a more significant initial injury, or alternatively, a greater injury to the vascular endothelium and glycocalyx (Fig. 1, Panel C). With regards to the fluid resuscitation in relation to Parkland Formula, Figure 2 (Panel A) shows non-survivors received a smaller volume of resuscitation fluid when comparing all patients. Most patients received more fluid than calculated by the Consensus Formula (7.2 ± 7.5 mL kg⁻¹%TBSA). Although non-survivors received volumes in keeping with the Consensus Formula (4.1 \pm 4.2 mL kg⁻¹%TBSA), this was significantly less than survivors (8.4 \pm 8.1 mL kg⁻¹%TBSA). However, when comparing survivors and non-survivors with a TBSA involvement of 15-90% (and excluding pure inhalation injury), in Figure 2 (Panel B), similar volumes were given in each group. The evolution in daily and cumulative fluid balance is shown in Figure 3. Table 3 provides information on fluid intake and output. Non-survivors had more fluid intake, as well as a more positive daily and cumulative fluid balance at 48 hours (end of resuscitation period).

HEMODYNAMIC VARIABLES

Table 4 lists the hemodynamic and respiratory variables. In terms of assessing fluid resuscitation targets,

Variable	Total	Survivors (n = 41)	Nonsurvivors (n = 15)	P-value
Age (years)	43.1 ± 25.9	38.4 ± 24.9	55.9 ± 24.8	0.023
Weight (kg)	68.5 ± 28.3	66.2 ± 27.9	74.7 ± 29.3	0.324
Height (cm)	162 ± 30.9	160.3 ± 33.4	166.5 ± 23.4	0.512
BMI	24.5 ± 6.3	24.1 ± 6.2	25.6 ± 6.8	0.460
M/F	2.1	2.4	1.5	NS
Origin Burn injury				
Flame (n)	42.0	32.0	10.0	NS
Scald (n)	9.0	7.0	2.0	NS
Toxic (n)	5.0	2.0	3.0	NS
nhalation (n)	33.0	25.0	8.0	NS
SAPS II	43.5 ± 15.1	39 ± 12.5	55.6 ± 15.1	< 0.0001
APACHE II	15.8 ± 6.8	13.9 ± 5.7	20.8 ± 6.9	< 0.0001
Probability mortality	34.6 ± 25.1	27.2 ± 21.2	54.9 ± 24.1	< 0.0001
SOFA	6.4 ± 3.5	5.9 ± 3.1	7.8 ± 4	0.062
SOFA respiratory	1.3 ± 1.1	1.3 ± 1	1.5 ± 1.2	0.508
SOFA coagulation	0.3 ± 0.7	0.1 ± 0.3	0.8 ± 1.1	< 0.0001
SOFA liver	0.3 ± 0.6	0.2 ± 0.5	0.7 ± 0.8	0.013
SOFA cardiovascular	1.7 ± 1.4	1.4 ± 1.2	2.4 ± 1.5	0.015
SOFA neurologic	2.3 ± 1.8	2.5 ± 1.8	1.9 ± 1.8	0.254
SOFA renal	0.5 ± 1.2	0.5 ± 1.1	0.6 ± 1.4	0.704
Drgan failures (n)	1.2 ± 1	1.2 ± 0.9	1.4 ± 1.2	0.464
3SA (m²)	1.7 ± 0.5	1.7 ± 0.5	1.8 ± 0.5	0.402
%TBSA	24.9 ± 24.9	16 ± 15.1	49.1 ± 30.4	< 0.0001
^{3rd} degree (%)	12 ± 23.6	5.1 ± 9.5	30.8 ± 37.5	< 0.0001
2 nd degree deep (%)	5 ± 8.1	5.3 ± 6.7	4.3 ± 11.4	0.680
2 nd degree superficial (%)	7.7 ± 14	5.4 ± 5.3	14.1 ± 25	0.038
AP high (mm Hg)	9.9 ± 3	9.4 ± 3.1	11.3 ± 2.4	0.033
AP mean (mm Hg)	10.3 ± 2.7	9.5 ± 2.2	12.6 ± 2.7	< 0.0001
AP max (mm Hg)	16.4 ± 4.9	15.2 ± 4.6	19.6 ± 4.2	0.002
AH	44.0	29.0	15.0	.014
AH treatment	24.0	17.0	7.0	NS
IAH resolution	25.0	24.0	1.0	< 0.0001
ACS	16.0	6.0	10.0	< 0.0001

Table 2. Patient demographics

transpulmonary thermodilution measurements (performed in 23 patients) confirmed a higher EVLWI in the non-survivors (for both the mean and maximum readings). Figure 4 (Panel A) shows the evolution of EVLWI in survivors vs. non-survivors. The global ejection fraction (GEF) was lower in non-survivors (Figure 4, Panel B). The GEDVI was significantly higher in non-survivors on day 2 (830 ± 161 vs. 678 ± 116 mL m⁻² with *P* = 0.021) and day 5 (891 ± 242 vs. 713 ± 96 mL m⁻² with *P* = 0.046), suggesting that fluid overload may be associated with worse outcomes. The other PiCCO variables, including CI, and SVV were not significantly different. The average dose was 4.5 ± 3.9 ug $kg^{-1}min^{-1}$ for dobutamine and 0.1 \pm 0.1 ug $kg^{-1}min^{-1}$ for norepinephrine.

ABDOMINAL HYPERTENSION

Forty-four patients (78.6%) developed IAH and 16 (28.6%) suffered ACS based on the WSACS definitions. Seventeen patients had IAH on admission, while the others (n = 27) developed it during their ICU stay (on average day 2.6 \pm 2). Patients with ACS (on average diagnosed after 5.6 \pm 3.8 days) had higher TBSAs burned (39.6 \pm 26.4 vs. 21.7 \pm 23.6%, *P* = 0.03) and higher cumulative fluid balances (11.4 \pm 15.8 L vs. 4.3 \pm 3.6 L, *P* = 0.08). On admission, the APP was

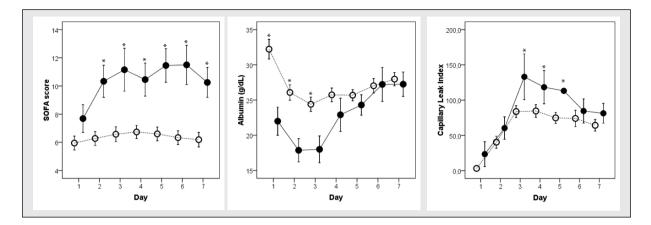


Figure 1. Day-by-day evolution of SOFA score, albumin and capillary leak index in survivors (open circles) vs non-survivors (closed circles) during the first week of stay. *indicates P < 0.05. **Panel A.** Evolution of SOFA score; **Panel B.** Evolution of albumine levels (g L⁻¹); **Panel C.** Evolution of capillary leak index in 33 patients with inhalation injury

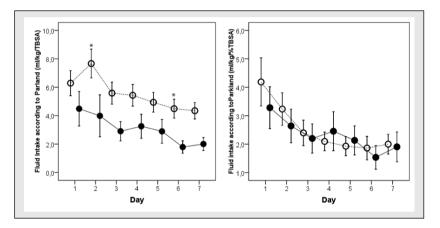


Figure 2. Daily fluid intake according to Parkland Consensus Formula. **Panel A**. Daily fluid intake according to Parkland formula (mL kg⁻¹%TBSA) in all patients survivors (open circles) and nonsurvivors (closed circles), * indicates P < 0.05; **Panel B**. Daily fluid intake according to Parkland formula (mL kg⁻¹%TBSA) in subgroup of adult patients with %TBSA between 15 and 90% (excluding isolated inhalation injury), survivors (open circles) and nonsurvivors (closed circles), * indicates P < 0.05

50.5 ± 9.4 mm Hg and during the ICU stay the IAP_{max} was 15.7 ± 5.2. The again, happy with either maximum or maximal. Change to maximum as it is a finite value. IAP was reached after 4.7 ± 3.4 days. Non-survivors had higher IAP_{low}, IAP_{high}, IAP_{mean}, and IAP_{max} recordings. Notably, the MAP_{low} and APP_{low} were all lower in the non-survivor group. Intra-abdominal pressure was uniformly higher in non-survivors, with a concomitant lower APP. The TBSA burned correlated well with the mean IAP (R = 0.34, P = 0.01) (Fig. 5). Patients with ACS had a significantly higher risk of death (Fig. 6, Panel A).

MEDICAL MANAGEMENT

Specific treatment for IAH was performed in 24 patients. In 8 patients with IAH this was done by sedation and the use of neuromuscular blockers. All 16 patients with ACS received treatment, and 3 underwent decompressive laparotomy. Two of these patients died despite the surgical intervention. The remaining 13 ACS patients were managed with medical therapies (paracenthesis in 5, diuretics in 3, gastric suctioning in 2, stool protocol in 8, renal replacement therapy with net ultrafiltration in 1). A total of 19 interventions were performed and were successful in removing 2.2 ± 1.3 L of body fluids. This resulted in a substantial decrease in IAP and CVP measurements, together with improved oxygenation and urine output (Table 5). All patients in whom IAH resolved survived to 28 days (P < 0.0001). The cumulative survival for those patients that did not have IAH resolution was only 36.5% (Fig. 6, Panel B).

USE OF ICU RESOURCES

When comparing survivors and non-survivors, expectantly as expected, ICU (26.6 ± 28.1 vs. 16.3 ± 16.2) and hospital length of stay (59.9 ± 81.2 vs. 17.1 ± 15.9) was longer in survivors. The number of ventilator free days was also not significantly different

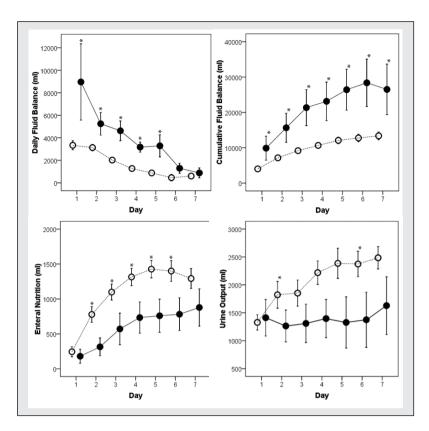


Figure 3. day-by-day evolution of fluid management in survivors (open circles) and nonsurvivors (closed circles), * indicates P < 0.05. Panel A. Daily fluid balance (mL); Panel B. Cumulative fluid balance (mL); Panel C. Daily enteral nutrition amount (mL); Panel D. Daily urine output

Variable	Total	Survivors (n = 41)	Nonsurvivors (n = 15)	P-value
Intake (mL)	6582.4 ± 8301	4888.1 ± 3079.8	11213.5 ± 14567.7	0.01
Enteral Nutrition (mL)	226.5 ± 380.2	244.6 ± 396.8	179.8 ± 345.4	0.622
Consensus (mL kg ⁻¹ %TBSA)	7.2 ± 7.5	8.4 ± 8.1	4.1 ± 4.2	0.056
Total intake (mL kg ⁻¹ , 48 hrs)	196.1 ± 125	178.1 ± 95.9	244.1 ± 176.9	0.081
Gastric output (mL)	200.7 ± 197.3	166.8 ± 191.9	302.4 ± 196.6	0.19
Urine output (mL)	1368.4 ± 980.1	1317.7 ± 851.6	1506.9 ± 1293.7	0.527
Urine output (mL kg ⁻¹ hr ⁻¹)	0.9 ± 0.7	1 ± 0.7	0.9 ± 0.6	0.639
Fluid Balance (mL)	4932.2 ± 7824.1	3289.3 ± 2555.4	9422.8 ± 13868.3	0.008
Cumulative FB (mL, 48 hrs)	5682.4 ± 7989.4	3954.9 ± 2953.2	10404.3 ± 13900.1	0.006

Table 3. Flui	d intake and output
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in the non-survivor group. However, when comparing those that developed IAH with those that did not in the survivor group, the latter had significantly more ICU free days, hospital free days, and ventilator free days (Table 6). Moreover, patients without IAH were weaned off the ventilator much quicker (Fig. 6, Panel C).

DISCUSSION

INCIDENCE OF IAH/ACS

The treatment of physiological shock related to burn injuries is most often based on empirical fluid resuscitation

formulae. This practice is still considered a reasonable initial approach and many formulae have been developed for this purpose. The Parkland Formula, now recognized as the Consensus Formula, has been the favoured technique since its introduction by Baxter and Shires in 1968 [22]. However, a correlation between IAP and total administered fluid volume has been reported [8, 23]. Patients with severe burns are at increased risk of developing (secondary) IAH and ACS due to the large volume of resuscitation fluid, decreased abdominal wall compliance, and increased capillary leakage,

Table 4. Cardiovascular and respiratory parameters

Variable	Total	Survivors (n = 41)	Nonsurvivors (n = 15)	P-value
Cardiovascular drugs				
Dobutamine (y)	4.5 ± 3.9	2.7 ± 0.6	5.9 ± 4.9	0.323
Noradrenaline (y)	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.082
Capillary leak				
EVLWI mean (mL kg ⁻¹ PBW)	9.6 ± 3.3	8.1 ± 1.8	11.2 ± 3.8	0.017
EVLWI max (mL kg ⁻¹ PBW)	14.6 ± 8.2	10.9 ± 2.2	18.8 ± 10.4	0.017
Day Max	4.6 ± 3.3	4.3 ± 2.3	5 ± 4.3	0.599
CRP (mg dL ⁻¹)	3.4 ± 6.6	2.7 ± 6.1	5.3 ± 7.7	0.197
Albumin (g L ⁻¹)	29.2 ± 9.7	31.9 ± 9	22 ± 7.7	< 0.0001
CLI	23.3 ± 52.7	15.1 ± 43.6	45.6 ± 68.8	0.053
Hemodynamic parameters				
HR (bpm)	106.9 ± 30.8	107.4 ± 31.8	105.4 ± 28.6	0.841
CVP (mm Hg)	13.6 ± 4.5	13.4 ± 4.8	14.3 ± 3.5	0.584
MAP low (mm Hg)	61.1 ± 8.8	63 ± 8.5	56.1 ± 7.9	0.008
APP low (mm Hg)	51 ± 9.4	53.4 ± 8.6	44.5 ± 8.5	0.001
Respiratory variables				
RR	17.4 ± 5.6	17.2 ± 5.6	18.2±6	0.541
TV (mL)	480.5 ± 183.8	483.2 ± 189.4	471.5 ± 171.9	0.849
Pplat (cmH ₂ O)	22.4 ± 5.2	21.2 ± 4.3	26.3 ± 6.1	0.002
PEEP (cmH ₂ O)	6.7 ± 2.2	6.2 ± 1.9	8.1 ± 2.5	0.008
MV (L min⁻¹)	7.6 ± 2.6	7.4 ± 2.3	8.4 ± 3.5	0.255
Cdyn (mL cmH ₂ O ⁻¹)	31.8 ± 12.9	33.5 ± 13	26.2 ± 11.6	0.091

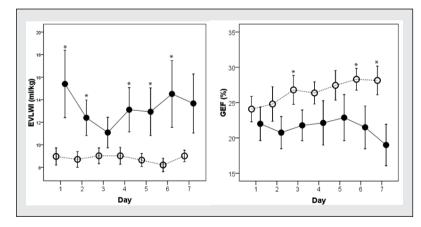


Figure 4. Evolution of transpulmonary thermodilution obtained parameters. **Panel A.** Day-by-day evolution of EVLWI in survivors (n = 12, open circles) vs non-survivors (n = 11, closed circles) in 23 patients with PiCCO monitoring, * P < 0.05; **Panel B.** evolution of global ejection fraction (GEF) in non-survivors (closed circles) and survivors (open circles). *P < 0.05

bowel oedema and other factors [24–33]. Oda *et al.* concluded that fluid resuscitation in excess of 300 mL kg⁻¹24h⁻¹ carries a high incidence of complications as a consequence of ACS [8]. Ivy *et al.* explored the relationship between the amount of fluid administered and IAP [34]. The correlation

demonstrated an IAP of 24.4 mm Hg when resuscitation with 250 mL kg⁻¹ was performed [34]. Interpreting these results, the Consensus Formulae requires a TBSA burn of 50% to achieve such amounts of fluid resuscitation. ACS complicates fluid resuscitation further since it causes urinary out-

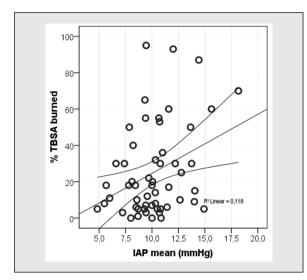


Figure 5. Correlation plot between mean IAP and %TBSA

put to become an inaccurate guide to fluid administration [35–37]. Central venous pressure (CVP) is also not a suitable tool to guide fluid resuscitation during shock caused by burns [38]. The total circulating blood volume could be an ideal guide to resuscitation [39]. However, a previous study found goal-directed therapy by invasive monitoring, as compared to Baxter's empiric resuscitation formula, caused a significant increase in the volume of fluid administration but did not improve preload or cardiac output parameters [18]. Thus, managing the appropriate volumes of resuscitation fluid is challenging. IAH/ACS is currently expected to be a life-threatening complication in severely burned patients.

There are a relatively small number of patients in previously conducted studies. In our study, intra-abdominal hypertension (IAH), defined as a sustained IAP > 12 mm Hg, was present in 44 (78.6%) patients and 16 (28.6%) patients developed ACS. To the best of our knowledge, we report the longest series of burn patients being evaluated for IAH and ACS.

Our study confirms that SAPS II, APACHE II, the TBSA burned, percentage of full-thickness 3rd degree burns, IAP (low, high, mean and max), CLI, EVLWI (mean and max), PEEP, P_{olat}, total fluid intake, daily and cumulative fluid balance were all significantly higher in non-survivors, while APP and albumin were significantly lower. The percentage of TBSA burned correlates with mean IAP. The combination of a high CLI, positive (daily and cumulative) fluid balance, high IAP, high EVLWI and low APP, correlate with a poor outcome. Most patients received more fluid than initially calculated by the Consensus Formula (7 \pm 7.5 mL kg⁻¹%TBSA) and remarkably, non-survivors received less (3.9 \pm 4.1 vs. 8.3 \pm 8.2 mL kg⁻¹%TBSA). This may be explained by a shortened time for fluid administration due to early death.

OUTCOME

The high mortality rate observed in the present study can probably be explained by the large number of inhalation injuries, advanced age and larger TBSA burned in nonsurvivors [40]. The comparison between survivors and nonsurvivors shows some remarkable findings. In addition, the burden of burn injuries on available critical care resources can be seen in the duration of ICU and hospital stays (23.9 \pm 25.7 and 48.4 ± 72.3 respectively). These numbers, together with the SOFA scores demonstrating the need for organ support, highlight the resource and financial implications of burn injuries, and the need to identify ways in which to improve burn care management and shorten hospital stays. The mortality in those developing ACS was significantly higher (10 out of 16 patients, 62.5%) when compared to those that did not (5 out of 40 patients, 12.5%). The mortality in those developing IAH (15 out of 44 patients, 34.1%) was also significantly higher than those who did not suffer from IAH (0 out of 12 patients, P = 0.014). Burn patients are at a substantial risk to develop IAH and ACS and this influences mortality.

Medical interventions, as demonstrated in this study, significantly reduced both the IAP and the CVP, improving oxygenation and urine output [41–44]. Appropriate monitoring and early medical interventions may alleviate the consequences of IAH and ACS, as well as affect outcome [5].

Non-survivors showed a higher capillary leak index, which once again may reflect a more significant initial injury, or alternatively, a greater injury to the vascular endothelium and glycocalyx [45, 46]. This may account for the greater decrease in albumin with less control over the regulation of

Table 5. Effect of medical management on organ	n function (19 interventions in 13 patients)
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	Before	After	P-value
AP (mm Hg)	17.8 ± 3.4	11.1 ± 3.5	< 0.0001
APP (mm Hg)	62.3 ± 13.8	69.1 ± 12.7	NS
CVP (mm Hg)	16.6 ± 5.5	12.8 ± 4.3	0.005
pO ₂ /F _i O ₂	251 ± 110	303.2 ± 114.2	0.01
Urine output (mL hr ⁻¹)	83.3 ± 75.3	208.4 ± 148.6	0.0003

	Total	No IAH (n = 11)	IAH (n = 29)	P-values
ICU free days	9.4 ± 8.3	16.4 ± 7.5	6.7 ± 7.1	< 0.0001
HOS free days	5.4 ± 7.2	10.6 ± 9.2	3.5 ± 5.7	0.006
MV free days	14.8 ± 8.5	20.8 ± 5.3	12.5 ± 8.4	0.004

Table 6. ICU and hospital free days in 40 survivors

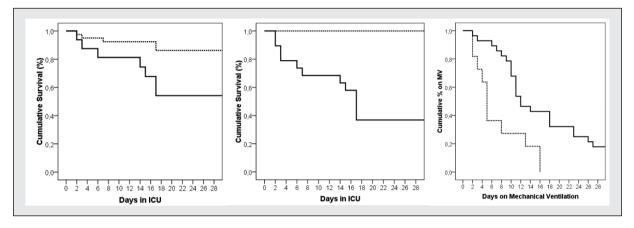


Figure 6. Kaplan Meier curves. **Panel A.** Cumulative 28 day survival, solid line ACS, dotted line no ACS (P < 0.0001); **Panel B.** Cumulative 28 day survival, solid line no IAH resolution, dotted line IAH resolution (P < 0.0001). All patients in whom IAH resolved survived at 28 days; **Panel C.** Cumulative percentage of patients on mechanical ventilation (solid line = IAH, dotted line is no IAH) (P = 0.001)

intravascular fluids due to the destruction of the glycocalyx. An ongoing inflammatory response, or one that is greater than that encountered in survivors may also account for the increased CLI and decrease in albumin.

The poor outcomes from burns patients who develop intra-abdominal hypertension and compartment syndrome is shown in Table 7. Including this study, the 42 publications show a marked variation in definitions of abdominal hypertension, compartment syndrome, inclusion criteria, and treatment methods. However, the outcomes remain poor. Only 8 of the studies are prospective, with the vast majority being observational, cohort studies, thus demonstrating the difficulty to design and run studies on this subject.

BURNS AND FLUIDS

Recent investigations, supported by our own preliminary results, have implied that the current practice in many burn centres is to infuse volumes greater than would be predicted by existing formulas. Until today, fluid restrictive regimes have not been shown to improve outcome in burn patients [47], although some have suggested a reduction in fluid volumes with restricted fluid regimens in burns [48, 49]. The data show that plasma-resuscitated patients maintained an IAP below the threshold of complications of intra-abdominal hypertension [14]. Oda *et al.* demonstrated that in patients with severe burn injury, hypertonic lactated saline resuscitation could reduce the risk of secondary ACS [2]. A further comparison evaluating the difference in survival between crystalloid resuscitation and fluid restrictive regimens has not yet been conducted. Unfortunately, future studies would need to be large, multi-centre trials that could enable the difference in survival on the basis of a bi-modal fluid resuscitation (early adequate followed by late conservative) to be evaluated [50]. To show a 10% difference in survival, with a power of 80% and expected *P*-value of 0.05, 900 patients would be required in each group, as previously stated [14].

PROGNOSIS

The results of this study support the hypothesis that (secondary) IAH and ACS are more prevalent in mechanically ventilated burn patients compared to other groups of critically ill patients [6, 24, 25]. Early implementation of medical interventions (as was performed in our study) is useful in improving IAP, oxygenation, and potentially venous return to the right side of the heart. Urine output improvement may reflect better renal perfusion. These interventions should become the standard of care, along with monitoring of IAP in all patients at risk of developing IAH and ACS. Failure to identify and manage IAH and ACS in burn patients will increase the risk of non-resolution of IAH/ACS and subsequent mortality.

Author	Year	Study model	Patients (n)	Type of patients	Inclusion TBSA	Mean TBSA (&/or range)	IAH treshold (mm Hg)	Mean IAP (range)	IAH (n)	IAH (%)	ACS (n)	ACS (%)	Treatment
Greenhalgh [29]	1994	٩	30	burns	56%	$56.2 \pm 3.6\%$	30	NR	12	40.0%	7	23.3%	PD/laparotomy
lvy [57]	1999	S	£	burns	20%	87.3% (74–98%)	25	45	ĸ	NA	ĸ	NA	Escharotomy
lvy [23]	2000	٩	10	burns	22%	46% (22–80%)	25	30 (9–44)	7	70.0%	2	20.0%	Sedation/laparotomy
Mayes [58]	2000	S	9	burns	20%	60% (20–91%)	NR	NR	assumed to be 6	assumed to be 100%	9	100.0%	DL
Corcos [42]	2001	S	£	burns	40%	60% (40–70%)	20	52 (36–82)	ĸ	NA	ŝ	NA	PD/laparotomy
Wilson [59]	2001	ß	٦	burns	20%	NA	Clinical	NA	NR	NR	-	NA	Escharotomy
Latenser [3]	2002	Я	13	burns	40%	58%	25	34 (26–42)	6	69.2%	4	30.8%	PD/laparotomy
Hobson [43]	2002	Я	10	burns	68%	71%	30	40 (30–50)	10	100.0%	10	100.0%	PD/laparotomy
Blinderman [60]	2002	ß	٦	burns	80%	NA	50	NA	۲	NA	-	NA	DL
Tsoutsos [61]	2003	٩	24	burns	35%	57.4% (37–85%)	14.7–18.3	17.1	10	41.7%	10	41.7%	Escharotomy
Pirson [62]	2004	CR	-	burns	53%	NA	22	NA	1	NA	1	NA	laparotomy
Rodas [30]	2005	R	-	5 trauma (1 burn)	70%	NA	Clinical	NA	NR	NR	1 burn + 4 others	NA	laparotomy
Oda [63]	2005	٩	36	burns	30%	49% (30–99%)	22	52±9	8	22.2%	8	22.2%	Escharotomy
Oʻmara [14]	2005	٩	31	burns	25% +inhalation or 40%	51 ± 12%	25	24.2 (9–42)	26	83.9%	4	12.9%	Sedation
Britt [64]	2005	S	10	mixed \$	40%	AN	clinical + IAP	40.6 (30–55)	only 7 measured	70.0%	10	NA	DL
Oda [8]	2006	Я	48	burns	30%	45.9% (25.2–96.5%)	22	NR	NR	NR	8	16.7%	Escharotomy
Kowal–Vern [33]	2006	Ж	29	burns	45.7%	NR	25	NR	22	75.9%	6	31.0%	PD/laparotomy
Jensen [32]	2006	S	4	3 burns, 1 TBI	65%	70%	22 + Clinical	NR	NA	NA	£	75.0%	laparotomy
Parra [44]	2006	ß	-	burns	%09	NA	34	NA	NA	NA	1	NA	PD/escharotomy
Ball [31]	2006	ß	-	burns	52%	NA	20	38	1	NA	1	NA	Escharotomy/DL
Küntscher [39]	2006	Я	16	burns	20%	46% (26–67%)	NR	NR	NR	NR	NR	NR	Escharotomy
Oda [2]	2006	£	36	burns	40%	65.2% (40–99%)	22	NR	13	36.1%	13	36.1%	Sedation/paralysis/ escharotomy
1 avic [65]	2006	ر د	~	hirne	7000		35			N I N			

Author	Year	Study model	Patients (n)	Type of patients	Inclusion TBSA	Mean TBSA (&/or range)	IAH treshold (mm Hg)	Mean IAP (range)	HH (ب	IАН (%)	ACS (n)	ACS (%)	Treatment
Hershberger [12]	2007	٣	25	burns	65%	46–84%	24	NR	25	100.0%	25	100.0%	Sedation/paralysis/ escharotomy
Oda [27]	2007	ж	38	burns	40%	NR	22*	14.6±7.3* to 34.36 ± 8.2	14	36.8%	14	36.8%	Sedation/paralysis/ escharotomy
Klein [66]	2007	Я	72	burns	44.5%	20–90%	NR	NR	NR	NR	3024	4.2%	NR
Muangman [67]	2007	S	Ŋ	burns	40%	61 ± 21% (40−90%)	AN	36±21 (10-60) #	2	100.0%	NA	NA	NA
Keramati [68]	2008	S	Q	burns (5 thermal, 1 electrical)	78%	37% (65–85%)	Clinical	39	Q	100.0%	9	100.0%	laparotomy
Ennis [69]	2008	Ъ	118	burns	30%	51% (33–69%)	NR	NR	NR	NR	12.98	11.0%	NR
Dulhunty [70]	2008	Я	80	burns	15%	$43\% \pm 19\%$	30	NR	NR	NR	12.8	16.0%	NR
Markell [71]	2009	ж	51	burns + trauma	48%	48% ± 19%	30	NR	NR	NR	32	62.7%	NR
Sanchez [72]	2009	٩	33	burns	20%	20–93%	12	NR	22	66.7%	ε	9.0%	NR
Poulakidas [73]	2009	S	£	burns	92%	92–95%	25	NR	n	NA	ε	NA	Escharotomy + DL
[hamm [74]	2009	ß	-	burns	11%	NA	NR	NA	۲	NA	1	NA	DL
Cartotto [75]	2010	Я	194	burns	15%	31% (15–81%)	NR	NR	NR	NR	7954	4.1%	DL
Lamb [76]	2010	ß	-	burns + trauma	33%	NA	NR	NA	1°	NA	1°	NA	DL
Rogers [77]	2010	ß	٦	burns	57%	NA	32	NA	٦	NA	٦	NA	DL
Mosier [78]	2011	Ж	153	burns	20%	46% (28–64%)	NR	NR	NR	NR	7038	4.6%	NR
Yenikomshian [79]	2011	Я	50	burns	20%	41% (23–65%)	NR	NR	NR	NR	4	8.0%	NR
Rocourt [80]	2011	Я	2	burns	15%	16.5%	25	NR	NR	NR	2	16.6%	PD
Ruiz–Castilla [81]	2014	٩	25	burns	20%	33% (25–58%)	12	Only baseline IAP reported	18	72.0%	1	4.0%	NR
McBeth [82]	2014	Я	(175)	burns	ISS>12	$31.4 \pm 20.9\%$ (5-95%)	12	NR	NR	NR	NR	NR	NR
			53	burns	ISS>12	35±16% (11–70%)	20	12.1 ± 4.2 (1–29)	12	22.6%	5	9.4%	3 x DL
Present study	2015	Ж	56	burns	20%	$24.9 \pm 24.9\%$	12	15.7±5.2	44	78.6%	16	28.6%	Medical/3x DL
Total			1286		41.6%	51.9% (32.9–81.5)	24 (12–30)	32.8 (18.1–47.4)	295	59.1% (22.2–100)	272	26% (4.2–100)	

INVASIVE CARDIOVASCULAR MONITORING

The CVP has proven to be a poor preload measurement in several studies on resuscitation of major burns [39]. The same holds true for urine output as a parameter to guide resuscitation. Pulmonary artery catheter (PAC) monitoring was considered the gold standard for assessment of cardiac output (CO), stroke volume (SV), systemic vascular resistance (SVR) and oxygen transport variables in the past. Recently, however, less invasive methods for the assessment of cardiac output and the measurement of intra-thoracic blood volumes have gained increasing acceptance in intensive care medicine [51, 52]. Although total circulating blood volume index (TBVI) guided burn resuscitation may be a superior method, its impact on outcome still needs to be demonstrated in future randomized studies [39]. In our study, PiCCO measured GEDVI was significantly higher in non-survivors on days 2 and 5. However, it is still unclear whether GEDVI is a useful outcome predictor or if it could be used as a resuscitation target.

PROPOSAL

Taking into account the findings of this study, we suggest an early, aggressive, goal-directed fluid resuscitation strategy. The results from this study support the idea that fluid restriction is not beneficial, and in fact more fluid than the Consensus Formula suggests is often administered. This phenomenon of fluid creep has emerged over the past few decades [53, 54], attributed by one author to an opioid creep [55]. It is yet to be established if the volume of fluid administered could be reduced by a combination of colloid and balanced salt solutions [56]. Once cardiovascular and perfusion parameters are achieved, the initial aggressive fluid strategy will need to be addressed and re-evaluated. Early monitoring of IAP in all burned patients, particularly those with TBSA burns of >20% (or > 15% in children) should become the standard of care. Early implementation of medical interventions to improve IAP should be attempted. Future research should also focus on evaluating the microcirculation and the effects of resuscitation on the glycocalyx.

LIMITATIONS

Firstly, the retrospective nature of the data analysis of this study may be regarded as a limitation. Secondly, there were no established protocols in the burn unit at the time the data was collected. Thirdly, there is no information on coagulation parameters, while an analysis on the possible role that blood products could have played in the outcome was not performed. Fourthly, the use of the PiCCO monitoring device was not standardized and, thus, not all patients have this cardiovascular data available which could have strengthened the findings regarding GEDVI. Moreover, no data was collected with regard to the strong ion difference (SID). Finally, albeit large in burns research publications, the total number of 56 patients included is still small.

CONCLUSION

Based on our preliminary results, we conclude that IAH and ACS has a relatively high prevalence in mechanically ventilated burn patients compared to other groups of critically ill patients. The percentage of TBSA burned correlates with the mean IAP. The combination of high CLI, positive (daily and cumulative) fluid balance, high IAP, high EVLWI and low APP, correlate with a poor outcome. Non-surgical interventions can lower IAP, CVP and can improve endorgan function. Non-resolution of IAH was related to a worse outcome. Future studies should focus on improved fluid resuscitation regimes, targeting microcirculation perfusion, with this group possibly benefitting from a bi-modal fluid model, favouring colloids rather than crystalloids.

ACKNOWLEDGEMENTS

- 1. The authors declare no financial disclosure.
- 2. Dr Wise declares that he has no financial or personal relationships that may have inappropriately influenced him in writing this paper. Dr De laet is member of the Executive Committee of the World Society on the Abdominal Compartment (WSACS) and current Secretary. Dr Malbrain is member of the Executive Committee of the World Society of the Abdominal Compartment (WSACS) and current Treasurer; he is member of the medical advisory board of Pulsion Medical Systems (Maquet Getinge group). The other authors have no possible conflicts of interest related to the content of this paper.

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