Incidence, Risk Factors, and Outcomes of Intra-Abdominal Hypertension in Critically Ill Patients-A Prospective Multicenter Study (IROI Study)

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Incidence, Risk Factors, and Outcomes of Intra-Abdominal Hypertension in Critically Ill Patients—A Prospective Multicenter Study (IROI Study)

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*See also p. 608.

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Objectives: To identify the prevalence, risk factors, and outcomes of intra-abdominal hypertension in a mixed multicenter ICU population.

Design: Prospective observational study.

Setting: Fifteen ICUs worldwide.

Patients: Consecutive adult ICU patients with a bladder catheter.

Interventions: None.

Measurements and Main Results: Four hundred ninety-one patients were included. Intra-abdominal pressure was measured a minimum of every 8 hours. Subjects with a mean intra-abdominal pressure equal to or greater than 12 mm Hg were defined as having intra-abdominal hypertension. Intra-abdominal hypertension was present in 34.0% of the patients on the day of ICU admission (159/467) and in 48.9% of the patients (240/491) during the observation period. The severity of intra-abdominal hypertension was as follows: grade I, 47.5%; grade II, 36.6%; grade III, 11.7%; and grade IV, 4.2%. The severity of intra-abdominal hypertension during the first 2 weeks of the ICU stay was identified as an independent predictor of 28- and 90-day mortality, whereas the presence of intra-abdominal hypertension on the day of ICU admission did not predict mortality. Body mass index, Acute Physiology and Chronic Health Evaluation II score greater than or equal to 18, presence of abdominal distension, absence of bowel sounds, and positive end-expiratory pressure greater than or equal to 7 cm H_2O were independently associated with the development of intra-abdominal hypertension at any time during the observation period. In subjects without intra-abdominal hypertension on

day 1, body mass index combined with daily positive fluid balance and positive end-expiratory pressure greater than or equal to 7 cm H_2O (as documented on the day before intra-abdominal hypertension occurred) were associated with the development of intra-abdominal hypertension during the first week in the ICU.

Conclusions: In our mixed ICU patient cohort, intra-abdominal hypertension occurred in almost half of all subjects and was twice as prevalent in mechanically ventilated patients as in spontaneously breathing patients. Presence and severity of intra-abdominal hypertension during the observation period significantly and independently increased 28- and 90-day mortality. Five admission day variables were independently associated with the presence or development of intra-abdominal hypertension. Positive fluid balance was associated with the development of intra-abdominal hypertension after day 1. (*Crit Care Med* 2019; 47:535–542)

Key Words: intra-abdominal hypertension; intra-abdominal pressure; prevalence; risk factors

Recent single-center studies have reported the presence of intra-abdominal hypertension (IAH) (1, 2) in 38–45% of all adult patients treated in an ICU setting (3–5). Previously published multicenter studies have included only selected patients (with an expected ICU stay > 24 hr) and observed even higher proportions of patients with IAH (6, 7).

IAH may lead to organ dysfunction and abdominal compartment syndrome (ACS) (1–11). However, research findings are conflicting as to whether IAH is independently associated with increased mortality (3–5, 7, 12, 13). Many risk factors have been associated with IAH, but the results have varied depending on the definitions used and the population studied (7, 10–16).

In summary, the actual prevalence, outcome, and risk factors of IAH are still unclear. To date, this is the first prospective multicenter observational study to include a large, consecutively enrolled mixed ICU population.

The objectives of this study were: 1) to identify the occurrence of IAH and the IAH severity grades on the day of ICU admission and during the observed period of ICU stay, 2) to investigate whether IAH is independently associated with increased 90-day mortality, and 3) to identify the factors associated with the development of IAH during an ICU stay.

MATERIALS AND METHODS

Patients and Measurements

The Ethics Committee of the South Metropolitan Health Service in Perth, Australia (13/20), approved the study with a waiver of informed consent, as the criteria set out by the Australian National Health and Medical Research Council were fulfilled. Subsequently, institutional ethics committees for each site approved the study. Only deidentified patient data were collected. The study was also approved and registered as an official Abdominal Compartment Society study (No 16, www.wsacs.org).

A detailed description of site selection, patient inclusion criteria, intra-abdominal pressure (IAP) measurements, and data collection is presented in **Supplemental Methods** (Supplemental Digital Content 1, http://links.lww.com/CCM/E253), and daily variables (documented each day until ICU discharge or 14 d) considered for regression analyses are presented in **Supplemental Table 1** (Supplemental Digital Content 2, http://links.lww.com/CCM/E254).

IAH and ACS were defined as previously described (2). The severity of IAH was graded as follows: grades I–IV were defined as IAP 12–15, 16–20, 21–25, and greater than 25 mm Hg, respectively (2).

Mean IAP for each patient on each study day was calculated, and patients were categorized as having IAH if they had at least 1 day with a mean IAP of 12 mm Hg or higher.

Maximum IAH grade was determined based on the highest mean IAP of any study day.

Primary IAH was defined as IAH in the setting of an injury or disease in the abdominopelvic region (2).

Sample Size Calculation and Statistical Analysis

Details on sample size calculation and statistical analysis are presented in Supplemental Methods (Supplemental Digital Content 1, http://links.lww.com/CCM/E253).

Missing data are reported in Supplemental Table 1 (Supplemental Digital Content 2, http://links.lww.com/CCM/E254).

The effect of different sites was estimated with the design effect formula (17) and controlled for by using stepwise regression analysis based on generalized estimating equations in all of our regression analyses.

RESULTS

This study included 491 patients from 15 sites (12 mixed, three surgical ICUs) (see flow diagram in **Supplemental Figure 1** (Supplemental Digital Content 3, http://links.lww.com/CCM/E256; **legend**, Supplemental Digital Content 8, http://links.lww.com/CCM/E260). Site descriptions are presented in **Supplemental Table 2** (Supplemental Digital Content 4, http://links.lww.com/CCM/E255). The design effect for sites for IAH on any study day was 5.6 and that for 90-day mortality was 2.2.

In 24 patients (4.9%), IAP was not measured on the day of ICU admission but was measured on subsequent days. Of the 467 patients in whom IAP was measured on the admission day, 159 (34.0%) had IAH. An additional 81 of 491 (16.5%) developed IAH later during their ICU stay (up to 14 study days) (**Fig. 1**). From day 7 onward, only an additional seven of 491 (1.4%) patients developed IAH. We therefore limited the observations between ICU days 2–7 to establish risk factors for the development of IAH during the ICU stay.

Altogether, 240 of 491 patients (48.9%) suffered from IAH during the observation period, nearly half of whom (46.3%) had Primary IAH. Although 114 of the IAH patients (47.5%) had IAP that remained between 12 and 15 mm Hg (IAH grade I) (**Fig. 2**), ACS was noted in 31 patients (6.3%) in total, and in 19 patients (3.9%), ACS was present on the day of ICU admission. Decompressive laparotomy was performed in 13 patients (in one patient twice); open abdomen treatment was thereafter applied in 11 patients (10 with vacuum-assisted closure).

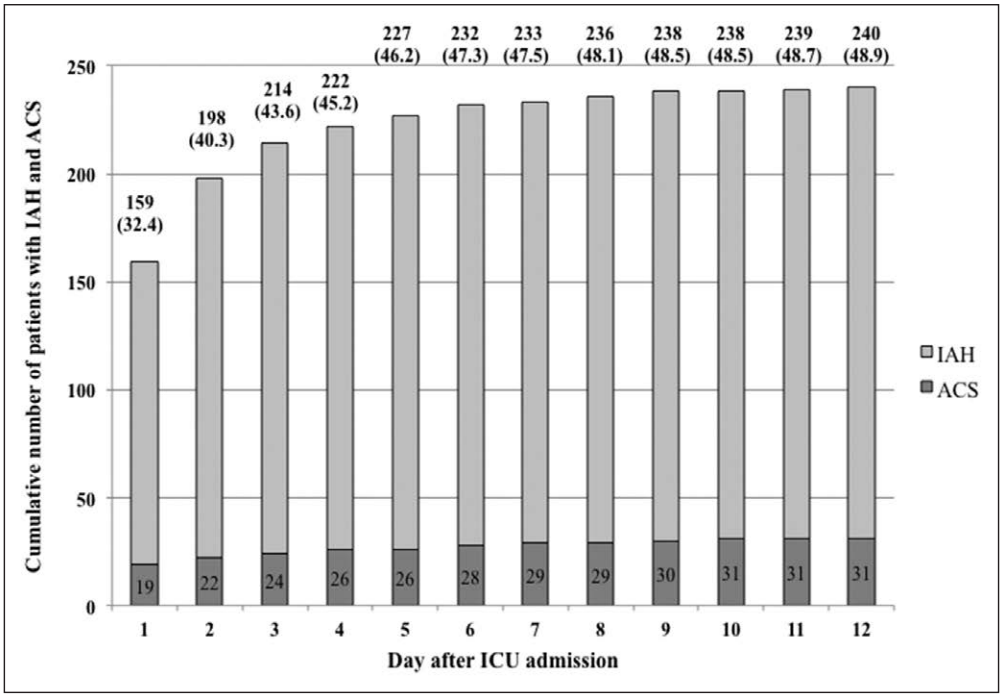

Figure 1. Cumulative prevalence of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS). Data for ACS are presented as number of patients. Data for IAH are presented as number of patients (%) and include ACS patients. Proportion of patients with IAH from the total study cohort (491 patients) is presented.

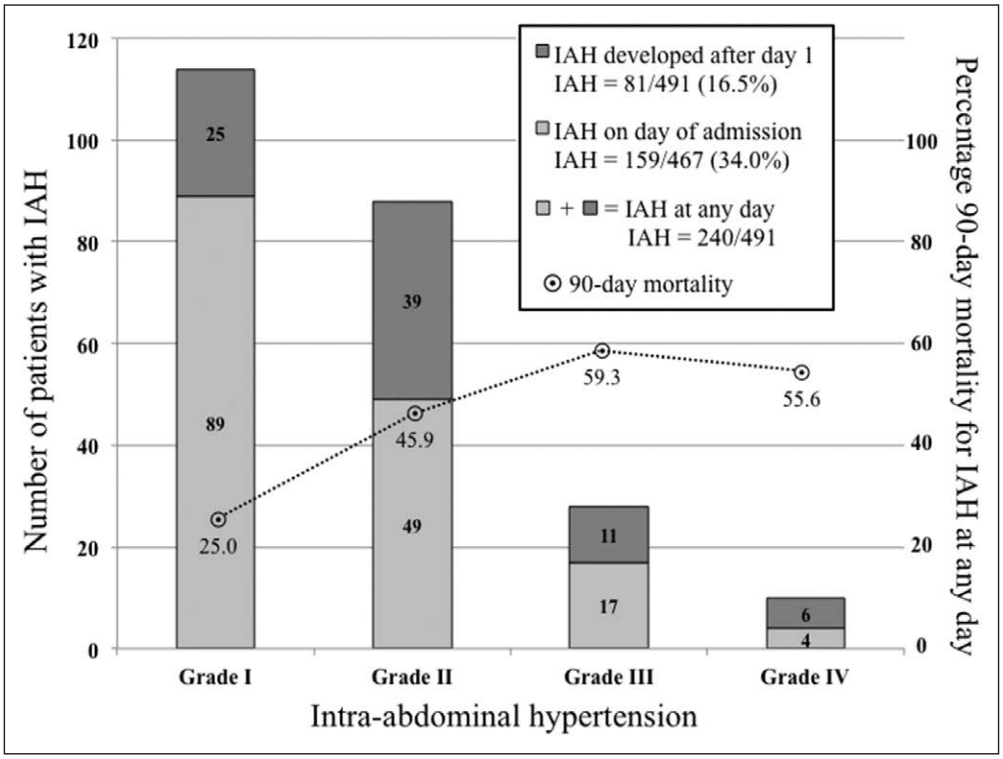

Figure 2. Proportion of patients with different intra-abdominal hypertension (IAH) grades and respective mortality rates. Data for number of patients per IAH grade. Mortality presented in relation to maximum IAH grade at any time during the ICU stay.

Baseline characteristics according to the presence or absence of IAH are shown in **Table 1**. IAH was observed in 99 medical patients (53.2%), in 86 emergency surgical patients (56.6%) and in 55 elective surgical patients (35.9%) ($p = 0.002$). There was no difference in IAH occurrence when comparing medical versus surgical patients (Table 1).

In total, 6,838 IAP measurements during 2,716 patient-days were recorded. Daily mean IAPs in mechanically ventilated and spontaneously breathing patients are presented in **Supplemental Figure 2** (Supplemental Digital Content 5, http://links.lww.com/CCM/E257; legend, Supplemental Digital Content 8, http://links.lww.com/CCM/E260).

IAH and Outcome

Both 28- and 90-day mortality were significantly higher in patients with IAH than in patients who never developed IAH (Table 1). The grade of IAH was inversely related to outcome (Fig. 2). The mortality of ACS was 67.7% at 28 days and 75.9% at 90 days. Of all nonsurvivors, 46.3% of patients without IAH, 43.8% of patients with IAH, and 68.4% of patients with ACS died during the first 7 days of the observation period.

Stepwise regression analyses revealed that both the presence of IAH during ICU stay and its maximum grade carry a significant risk of mortality. Presence of IAH on the day of ICU admission, regardless of grade, did not demonstrate any significance in mortality prediction. The best models for 90- (**Table 2**) and 28-day mortality (**Supplemental Table 3**, Supplemental Digital Content 6, http://links.lww.com/CCM/E258) prediction included maximum IAH grade. However, IAH on any study day regardless of grade was also identified as an independent predictor of mortality. In the regression analysis model of 28-day mortality, the presence of IAH was less predictive than maximum IAH grade, whereas models with IAH

TABLE 1. Admission Day Variables and Outcome Data

Variables	All	No IAH	IAH			*p* No IAH vs IAH Ever
			IAH Ever	IAH on Day of ICU Admission	IAH Occurred After Day1	
n (%)	491 (100)	251 (51.1)	240 (48.9)	159 (32.4)	81 (16.5)	
Age, median (IQR)	61 (18–94)	62 (20–91)	61 (49–72)	59 (21–94)	62 (20–86)	0.960
Male gender, *n* (%)	276 (56.2)	131 (52.2)	145 (60.4)	96 (60.4)	49 (60.5)	0.066
Body mass index, kg/m^2, median (IQR)	26 (23–31)	25 (23–29)	28 (24–32)	27 (25–32)	28 (24–32)	< 0.001
Surgery, *n* (%)	305 (62.2)	164 (65.3)	141 (58.7)	102 (64.2)	42 (51.9)	0.133
Abdominal surgery, *n* (%)	126 (25.7)	95 (37.8)	89 (37.1)	**68 (42.8)**[a]	**21 (25.9)**	0.861
Mechanical ventilation, *n* (%)	317 (64.6)	140 (55.8)	177 (73.8)	112 (70.4)	65 (80.2)	< 0.001
Vasopressors, *n* (%)	220 (44.8)	96 (38.2)	124 (51.7)	85 (53.5)	39 (48.1)	0.002
Acute Physiology And Chronic Health Evaluation II score, median (IQR)	16 (11–23)	15 (10–19)	19 (13–25)	19 (15–26)	20 (14–28)	< 0.001
Fluid balance in the ICU, L, median (IQR)	2.7 (2.0–4.4)	2.5 (1.8–4.1)	3.1 (2.1–4.5)	3.1 (2.2–5.1)	3.3 (1.9–4.9)	0.001
Central venous pressure, mm Hg, median (IQR)	10 (7–15)	8.0 (5–12)	13 (9–17)	13 (8–11)	14 (11–18)	< 0.001
Lactate, mmol/L, median (IQR)	2.0 (1.2–3.5)	1.8 (1.1–2.9)	2.4 (1.3–4.3)	2.6 (1.6–5.9)	2.2 (1.2–3.2)	0.001
Sequential Organ Failure Assessment score, median (IQR)	5.0 (3.0–9.0)	4.5 (2.0–7.0)	7 (4.0–10.0)	8.0 (5.0–11.0)	8.0 (5.0–9.0)	< 0.001
28-d mortality, *n* (%)	92 (18.7)	27 (10.8)	65 (27.1)	45 (28.5)	20 (24.7)	< 0.001
90-d mortality, *n* (%)	129 (26.3)	41 (16.3)	88 (36.7)	59 (38.6)	29 (36.3)	< 0.001
Mechanical ventilation duration, d, median (IQR)	3 (1–8)	1 (1–5)	5 (1–10)	4 (1–10)	6 (3–13)	< 0.001
ICU stay, d, median (IQR)	5 (2–12)	3 (2–8)	7 (3–13)	6 (3–13)	7 (4–15)	< 0.001
Hospital stay, d, median (IQR)	17 (9–30)	15 (8–26)	18 (11–32)	18 (9–32)	19 (15–33)	< 0.001

IAH = intra-abdominal hypertension, IQR = interquartile range.

[a]Significant difference in comparison of "IAH on day of ICU admission" vs "IAH occurred after day 1".

Boldface values indicate comparisons with significant difference.

presence and maximum IAH grade performed similarly for the prediction of 90-day mortality. The best model for prediction of 28-day mortality included admission day lactate, fluid balance, presence of sepsis, neurologic and hematologic Sequential Organ Failure Assessment subscores, and maximum IAH grade during the ICU stay (Supplemental Table 3, Supplemental Digital Content 6, http://links.lww.com/CCM/E258).

Patients with IAH had longer ICU and hospital lengths of stay, as well as longer duration of mechanical ventilation, than patients without IAH (Table 1).

Risk Factors for Having IAH During the Observation Period

Thirty-eight of 64 admission day characteristics were significantly different between the patients with and without IAH. The risk factors that were considered for entry in the regression analysis can be found in Supplemental Table 1 (Supplemental Digital Content 2, http://links.lww.com/CCM/E254), together with details on missing data, and cutoff values separating non-IAH versus IAH patients in our study cohort. The regression analysis identified admission day variables, including BMI greater than or equal to 27 kg/m^2, Acute Physiology And Chronic Health Evaluation (APACHE) II greater than or equal to 18, presence of abdominal distension, absence of bowel sounds, and positive end-expiratory pressure (PEEP) greater than 7 cm H_2O, as being independently associated with IAH (**Table 3**). Eleven patients (12.8%) developed IAH despite the absence of these factors.

Risk Factors for Patients Developing IAH During Their ICU Stay (Days 2–7)

Independent risk factors for the development of IAH beyond the ICU admission day included BMI, daily positive

TABLE 2. Stepwise Regression Analysis for 90-Day Mortality Prediction

Variables	OR	2.5%	97.5%	*p*	*n* (%) of Patients[a]
(Intercept)	0.031	0.015	0.064	< 0.0001	
Acute Physiology And Chronic Health Evaluation II	1.079	1.034	1.126	0.0005	
Maximum IAH grade I	1.098	0.583	2.067	0.7732	114 (23.2)
Maximum IAH grade II	2.251	1.200	4.223	0.0115	88 (17.9)
Maximum IAH grade III	4.436	1.444	13.634	0.0093	28 (5.7)
Maximum IAH grade IV	1.594	0.440	5.771	0.4775	10 (2.0)
Sepsis	3.759	2.223	6.357	< 0.0001	108 (22.0)
Neuro SOFA 1	2.409	1.071	5.420	0.0335	60 (12.2)
Neuro SOFA 2	0.977	0.357	2.672	0.9639	45 (9.2)
Neuro SOFA 3	3.923	1.833	8.396	0.0004	39 (7.9)
Neuro SOFA 4	3.317	1.623	6.781	0.0010	72 (14.7)

IAH = intra-abdominal hypertension, OR = odds ratio, SOFA = Sequential Organ Failure Assessment.
[a]Proportion of patients in this category from total cohort.
Quasi-likelihood information criterion: [1] 393.6315. Admission day variables are combined with maximum IAH grade during the ICU stay.

TABLE 3. Stepwise Regression Analysis for Associated Variables of Intra-Abdominal Hypertension

Admission Day Variables	OR	2.5%	97.5%	*p*
(Intercept)	0.276	0.181	0.420	< 0.0001
Body mass index ≥ 27 kg/m^2	1.937	1.168	3.210	0.010
Acute Physiology And Chronic Health Evaluation II ≥ 18 points	2.768	1.807	4.240	< 0.0001
Abdominal distension	3.191	1.503	6.773	0.003
Absence of bowel sounds	1.731	1.013	2.957	0.045
Positive end-expiratory pressure ≥ 7 cm H_2O	2.339	1.351	4.048	0.002

OR = odds ratio.
Quasi-likelihood information criterion: [1] 485.8979.

fluid balance, and PEEP greater than 7 cm H_2O (the latter two documented on the day before IAH occurred) (**Supplemental Table 4**, Supplemental Digital Content 7, http://links.lww.com/CCM/E259).

DISCUSSION

The present study is the first multicenter prospective observation on prevalence, risk factors, and outcome of IAH among the consecutive patients admitted to the ICU. The results partly confirm the findings of previous studies but also add some important new insights to the field.

Prevalence of IAH

The prevalence of IAH during the first 24 hours of admission was 34%, which is comparable with the result of a previously published multicenter study (7). However, this study included only patients with an expected ICU stay greater than 24 hours (7). Consecutive patients admitted to the ICU were studied in several recent single-center studies (3–5). Only one of these studies reported the prevalence of IAH on the day of ICU admission and found a similar prevalence (30%) as our study (5).

The daily dynamics of IAP have been presented in some previous studies (7, 12), whereas cumulative prevalence (5, 12) and risk factors of IAH (4, 5, 15) have been described in detail in only single-center studies.

Similar to the most recent single-center report (5), our study revealed that in IAH patients, IAH was not present in one third of patients on their admission day but developed after day 1. In keeping with other studies, the occurrence of lower IAH grades is more common than the occurrence of higher grades of IAH (Fig. 2).

The cumulative prevalence of ACS in our study was relatively high (6%), contradicting the recent suggestion by

Balogh et al (18) that ACS is a disappearing syndrome (18). However, a recent single-center study by Murphy et al (5) reported ACS in 2.8% of study patients. The most likely explanation for the cumulative prevalence of ACS in our study being twice that of the study by Murphy et al (5) is the case mix in our multicenter study that included some sites exclusively admitting patients with the highest illness severity and a very high prevalence of IAH (Supplemental Table 2, Supplemental Digital Content 4, http://links.lww.com/CCM/E255). Other sites admitted less sick patients with a significant proportion of patients being admitted after elective major surgery and presenting without acute organ failure. Such centers reported less IAH and a smaller proportion of ACS. The observed design effects reflect greater heterogeneity among the sites than expected and confirm that our case mix is clearly different from recent single-center studies including consecutive patients (3–5).

IAH and Outcome

IAH has been shown to be associated with adverse outcomes in several studies (5, 7, 12, 13), but some single-center studies have not confirmed this finding (3, 4). Severity/grade of IAH may explain the contradictory observations regarding mortality related to IAH in the literature. The overall effect of IAH on outcome may be a function of IAH severity because higher IAH grade is associated with higher mortality and vice versa. Accordingly, a site admitting less severe patients and observing only a few cases of IAH above grades I and II is likely to miss changes in mortality independently related to IAH. Our current study supports the differential impact of IAH grades on mortality (Table 2 and Fig. 2; and Supplemental Table 3, Supplemental Digital Content 6, http://links.lww.com/CCM/E258). Earlier observations (4, 5) have shown that IAH grade I (12–15 mm Hg) may not increase mortality. It is possible that IAH to some degree (grade I, and possibly in some cases also grade II) just mirrors the severity of the underlying disease and its treatments while not by itself having an additional deleterious physiologic effect or leading to worse outcomes compared with higher grade IAH.

Interestingly, in our study, IAH grade IV was associated with lower mortality than grade III (Table 2 and Fig. 2). This finding is likely due to the small number of patients presenting with grade IV ($n = 10$) (Table 2; and Supplemental Table 3, Supplemental Digital Content 6, http://links.lww.com/CCM/E258). Our study, however, invites the discussion to consider the possibility of grouping grades III and IV together.

The severity of IAH needs to be considered when carrying out future research and in providing future treatment recommendations. More aggressive and invasive treatment strategies (e.g., deep sedation, hemofiltration to restore fluid balance) suggested by the Guidelines (2, 16) are probably justified only in patients with severe IAH (possibly grade II and above). However, the results of several experimental studies have shown a negative impact of IAH on organ blood flow occurring with IAP values as low as 10–15 mm Hg (19–22), supporting the pathophysiologic rationale for keeping the cutoff of IAH at 12 mm Hg. Several clinical studies have confirmed that an IAP of 12 mm Hg and above results in increased mortality (6, 7, 10–12). In contrast, Petro et al (23) introduced the term "permissible IAH", suggesting that presence of grades I–II IAH for a limited time period after elective surgery for ventral hernia repair does not negatively affect outcome. These conflicting results once again indicate the importance of further distinction between IAH severity grades instead of addressing IAH as a "yes-or-no" phenomenon. Furthermore, the absolute value of IAP alone is probably not an effective trigger for distinct therapeutic measures. It is important to consider the dynamics of IAP with the underlying disease when treating any patient or in the development of management recommendations (2, 16).

Risk Factors

Our study is the first prospective multicenter study investigating consecutive adult patients worldwide. This study provides detailed insight into the risk of IAH at admission to the ICU and the changing risks that arise during a patient's ICU stay. Similar to previous reports, BMI and disease severity (3–5, 15) were associated with IAH. Mechanical ventilation has been an inclusion criterion in several studies addressing IAH in the ICU (12, 15), but the most recent single-center study also identified mechanical ventilation as a risk factor for IAH (5). In our current study, mechanical ventilation as a yes/no variable, compared with categorization by PEEP greater than or equal to 7 cm H_2O, had less power in identifying the presence of IAH on the day of ICU admission or the development of IAH during the ICU stay. Additionally, independent associations were found with only subjectively assessable variables, such as abdominal distension and absent bowel sounds. In several cases, causality remains unclear and may differ case-by-case (e.g., does PEEP increases IAP or IAH necessitates higher PEEP, or are absent bowel sounds a sign of ileus leading to IAH or does IAH disturb bowel peristalsis?). BMI is, in this case, the only variable with a clearly unidirectional effect, although its role in determining outcome is not clear. Higher baseline IAP, as seen in obese patients, is possibly not a cause of adverse outcomes. In our analysis, BMI was the only identified risk factor that was not directly related to increased mortality in the univariate analysis. At this time, it is not clear whether different cutoffs for IAH should be used in obese patients.

An important finding of our study is that positive fluid balance, shown to be a risk factor for IAH in several studies (4, 5, 14), may be most relevant later in the ICU stay, following aggressive resuscitation, when resistance to fluid mobilization is present.

Strengths and Limitations

The main strength of this study is the multicentered contribution of ICUs from around the world enrolling consecutive patients and performing IAP measurements throughout the ICU stay. This multicenter worldwide design has strength in that it is more likely to capture a large range of current practices but, at the same time, has the potential weakness of not

being reproducible for individual centers. Our study was not powered to perform a meaningful post hoc subgroup analysis for different continents or patient severity groups. We did not assess limitations of care (e.g., do not resuscitate orders) that were applied during the study period, possibly affecting our results regarding the effect of IAH on mortality (24). Other limitations, also related to the multicenter and investigator-initiated design of the study, include a long period for site recruitment and relevant differences between the sites. These differences are reported in the article and their effect controlled by using a regression method that allowed for clustering. Other important strengths of the study include novel information regarding the development of IAH in critically ill patients after the day of ICU admission and outcome data beyond the ICU period (90-d mortality).

CONCLUSIONS

In our mixed ICU patient cohort, we found that almost half of all patients admitted to the ICUs worldwide developed IAH and that two thirds of those cases were already present on the day of ICU admission. Our data further demonstrated that IAH occurred twice as often in mechanically ventilated patients as in spontaneously breathing patients. Most importantly, the presence and severity of IAH during the first 2 weeks of the ICU stay significantly and independently increased 28- and 90-day mortality, whereas the presence of IAH on the day of ICU admission was insufficient to predict these adverse outcomes.

The admission day variables independently associated with the presence or development of IAH included BMI greater than or equal to 27 kg/m^2, APACHE II greater than or equal to 18, PEEP greater than 7 cm H_2O, presence of abdominal distension, and absence of bowel sounds. Positive fluid balance, in addition to BMI and PEEP, was associated with the development of IAH beyond the day of ICU admission.

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