Journal of Critical Care 43 (2018) 42–47

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Neuroscience

Risk factors and outcomes of critically ill patients with acute brain failure: A novel end point☆

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ARTICLE INFO

Keywords:
Delirium
Acute brain failure
ICU
Coma
Electronic digital signature
Risk factors

ABSTRACT

Objective: To determine the incidence, risk factors and outcomes of acute brain failure (ABF) in a mixed medical and surgical cohort of critically ill patients and its effect on ICU & hospital mortality.
Design: Observational electronic medical record (EMR) based retrospective cohort study of critically ill patients admitted to the ICU between 2006 and 2013.
Setting: Tertiary academic medical center.
Patients: Consecutive adult (>18 years) critically ill patients admitted to medical and surgical ICUs. Patients admitted to the Neuroscience, Pediatric and Neonatal ICUs were excluded.
Interventions: None.
Measurements and main results: ABF was defined by the presence of delirium (positive CAM-ICU) or depressed level of consciousness (by abnormal GCS and FOUR scores) in the absence of deep sedation (RASS < −3). Severity of ABF was categorized as grade I if there was delirium with GCS consistently >8 and grade II if the GCS was ≤8 with or without delirium during the ICU hospitalization. ABF duration was not used for this study. Univariate and multivariable analyses were used to access the factors associated with the development of ABF and its effect on short and long term mortality. Of 67,333 ICU patients included in the analysis, ABF was present in 30,610 (44.6%). Patients with ABF had an isolated delirium in 1985 (6.5%) patients, isolated depressed consciousness in 18,323 (59.9%), and both delirium and depressed consciousness in 10,302 (33.6%) patients. When adjusted for comorbidities and severity of illness ABF was associated with increased hospital (OR 3.47; 95% CI 3.19–3.79), and at one year (OR 2.36; 95% CI 2.24–2.50) mortality. Both hospital and one year mortality correlated with the increased severity of ABF. The factors most strongly associated with ABF were pre-admission dementia (OR 7.86; 95% CI 6.15–10.19) and invasive ventilation (OR 2.32; 95% CI 2.24–2.40) but older age, female sex, presence of liver disease, renal failure, diabetes mellitus, malignancy and COPD were also associated with increased risk of ABF.
Conclusions: ABF is a common complication of critical illness and is associated with increased short and long term mortality. The risk of ABF was particularly high in older patients with baseline dementia, COPD, diabetes, liver and renal disease and those treated with invasive mechanical ventilation.

1. Introduction

Delirium is characterized by a disturbance in attention and awareness which develops over a short period of time with an additional disturbance in cognition [1]. The prevalence of delirium ranges from 16% to 87% in ICU patients [2], with an incidence of up to 83% in mechanically ventilated patients as compared to 20% in non-ventilated patients

☆ Financial disclosure: The remaining authors have disclosed that they do not have any conflicts of interest.

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http://dx.doi.org/10.1016/j.jcrc.2017.08.028
0883-9441/

[3-5]. Multiple clinical complications have been associated with ICU delirium including unplanned extubation, self-removal of catheters, aspiration, reintubation, longer length of hospital stay, short and long term mortality, and long term cognitive impairment [6-10]. Patients experiencing ICU delirium have a 49% increased risk of remaining in the hospital on any given day compared to those without delirium [11], and every additional day of ICU delirium is associated with a 10% increase in the hazard of death within 1 year post ICU admission [12]. Estimated health care costs associated with delirium are a staggering $164 billion (2011) per year in the United States and over $182 billion (2011) per year in 18 European countries combined [13-16].

However, delirium only reflects alterations in the *content* of consciousness and by definition should only be assessed in patients who are sufficiently alert to respond to some questions. Critically ill patients often also have depression in the *level* of consciousness (i.e. drowsiness, stupor and coma) [17]. Therefore a correct evaluation of acute brain dysfunction in critically ill patients must consider both content and level of consciousness. As the level and content of consciousness may form part of the same spectrum, separating them as different endpoints may not be biologically or clinically reasonable. Hence we favor the use of a novel endpoint, which we propose to call Acute Brain Failure (ABF), to encompass alterations in the level or content of consciousness and to be used as an outcome measure in studies evaluating acute impairment of consciousness in critically ill patients. In a previous study we showed that ABF can be reliably identified from electronic medical records when compared with a gold standard of prospective examinations by specifically trained clinicians [18].

In this study we sought to determine the incidence, risk factors and outcome of ABF in a mixed medical and surgical cohort of critically ill patients.

2. Materials and methods

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Mayo Clinic Institutional Review Board (IRB) for the use of existing medical records of patients or their relatives who gave prior research authorization.

We included consecutive patients who were admitted to one of the following ICUs at Mayo Clinic in Rochester, Minnesota between January 1, 2006 and December 31, 2013; medical ICU, coronary care unit, two mixed medical surgical ICU and the cardiosurgical ICU. Patients admitted to the Neuroscience, Pediatric and Neonatal ICUs were excluded. Of note, in our practice, patients with traumatic brain injury are admitted to the Neuroscience ICU. We only included the index ICU admission episodes for each patient during the study.

2.1. ABF definition (Fig. 2)

In our practice, the Richmond Agitation Sedation Scale (RASS) is used in patients receiving sedative drugs and the Glasgow Coma Scale (GCS) and the Full Outline of Unresponsiveness (FOUR) score are used to assess level of consciousness in non-sedated patients (including sedation holidays). The Confusion Assessment Method for the ICU (CAM-ICU) is tested after ensuring that the patients are not too sedated to participate in the testing (i.e. CAM-ICU is not tested if the RASS score is −3 or lower). ABF was defined by the presence of delirium (positive CAM-ICU) or depressed level of consciousness (by two consecutive scores of GCS score <15 and/or FOUR score <16) in the absence of deep sedation (RASS <3) during the ICU stay. For ventilated patients, GCS score of <11 in ventilated patients and FOUR scores of <13 was considered abnormal. Severity of ABF was categorized as grade 0 (no ABF), grade I if there was delirium with GCS consistently >8, and grade II if the GCS was ≤8 with or without delirium during the ICU hospitalization.

Deeply sedated patients (defined by a RASS score −3 or lower) were excluded because a reliable neurological examination cannot be performed in these instances. We chose to use two consecutive GCS or FOUR scores for the identification of reduced level of consciousness because these scores are more susceptible to the residual effects of sedation and thus relying on a single abnormal score could falsely identify patients as having ABF. In our ICUs, GCS and FOUR scores are documented every 4 h or less and the CAM-ICU is documented every 8-hour shift.

2.2. Identification of patients with ABF in the EMR

All the ICU patients were identified through a validated prospective electronic medical record (EMR) database that retrieves variables for all ICU patients in near real-time known as “the ICU Data Mart”. The Data Mart uses Microsoft Structured Query Language (MS SQL, Microsoft, Redmond, WA). Steps of the development of the database, data security and validation of the demographics have been previously reported [19].

Since the GCS, FOUR, CAM-ICU and RASS score in the Data Mart are entered by the ICU nurses, it becomes extremely important that these scores are accurate and in concordance to the physician's evaluations. In order to validate this we conducted a prospective observational study in a population of 55 patients to validate the EMR based ABF definition variables (CAM-ICU, modified RASS, GCS and FOUR scores) with the physician assessments. The Pearson correlation of GCS, FOUR score and modified RASS scores were 0.87, 0.92 and 0.73 with a mean difference of 0.35, 0.21 and 0.33 respectively, which were not significant. The Kappa coefficient for the CAM-ICU scores was 0.86. Hence there was an excellent correlation between the nursing and physician assessments. The details of this study methodology and results are being reported in a separate paper [18].

Next, in order to derive and validate the ABF definition, we randomly selected 200 patients from our study cohort for definition derivation; these patients underwent simultaneous manual chart review by two reviewers [TDS and DRR] and electronic search using the Mayo Clinic Life Sciences System, a validated electronic medical record search tool. Mayo Clinic Life Sciences System is a clinical data warehouse, developed in collaboration with Mayo Clinic and IBM that allows automated clinical data extraction through a query tool called the Data Discovery and Query Builder [20]. The results were compared (with manual review being considered as the gold standard), and disagreements were adjudicated by a third reviewer (RK). Elements abstracted and compared during the search included RASS scores, GCS scores, FOUR scores, and CAM-ICU. The automatic search was done by an independent critical care researcher (R.K.).

The electronic search strategy was refined continuously through the addition or change of terms to enhance sensitivity and specificity to >90% in the derivation subset. The performance improved, when the flow sheet row data equal to “Eye Response (F, Motor Response (F, Brainstem Reflex, Respiration (F (for FOUR score)” where the patient's nurses chart FOUR score was added to the search query. To validate the automated electronic search, sensitivity and specificity were calculated through comparison to the reference standard of comprehensive manual medical record review in a validation subset in another 200 randomly selected patients in an independent population. The final sensitivity of EMR search for identification of ABF was 95.9% (95% CI, 85.9%–99.4%) and specificity was 94.1% (95% CI, 83.7%–98.7%).

2.3. Risk factors and outcomes

The ICU data mart was used to abstract the baseline characteristics, comorbidities and clinical variables from the electronic medical records [21]. Basic demographic data included age, sex, race and body mass index (BMI). The comorbidities that were abstracted included a past medical history of hypertension, diabetes mellitus, diabetes with complications, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular accident, hemiplegia/paraplegia, asthma or chronic obstructive pulmonary disease (COPD), peptic ulcer, moderate/severe liver disease, cirrhosis, renal failure, and malignancy. During the ICU admission, the use of invasive or noninvasive

ventilation, length of ventilation and the length of ICU stay were also recorded. A Charlson comorbidity index (CCI) was calculated based on a previously validated algorithm at our hospital [22]. Acute Physiology and Chronic Health Evaluation III (APACHE III) at admission and Sequential Organ Failure Assessment (SOFA) score using variables collected within the first 24 h were also derived using the previously validated computerized automated systems at our institution [19,23,24]. ICU, hospital length of stay and 30 day, one year mortality were obtained from the validated EMR registry (Fig. 1).

2.4. Statistical considerations

We calculated sensitivity and specificity of the automated electronic note search strategy on the basis of comparisons of test results and the reference standard in both the derivation and validation patient subsets. The 95% confidence intervals were calculated with an exact test for proportions. For quantitative variables, data are presented as median (interquartile range) and for qualitative data as frequency (percentage). Patients were categorized into two groups of presence and absence of ABF based on our definition as discussed above. Univariate analyses and multivariate analyses were used to determine the group differences, validate ABF as a significant factor for predicting mortality and to determine the factors predisposing to the development of ABF. The categorical data were initially assessed using the chi-square test while Student *t*-test or Mann-Whitney test was used to analyze continuous variables as applicable. For comparing the three cohorts in the ABF severity scale, one-way Analysis of Variance (ANOVA) or Kruskal-Wallis test was used for continuous variables as applicable and chi-square test was used for categorical variables. All the variables which were found to be statistically significant on univariate analyses were then entered into a multivariable logistic regression analyses for the final analyses. In all the analyses, p values of ≤0.05 were considered statistically significant. AUROC were constructed to discriminate the ability of ABF, delirium only and abnormal GCS/FOUR score only to predict ICU and hospital mortality while r-squares were calculated for the endpoints of ICU and hospital length of stay. AUROC were also constructed for different models for measuring the severity and the final severity model was determined by comparison of the AUROC using methodology previously described [25]. Statistical analyses were performed using JMP 11.0.0 software (SAS Institute, Cary, NC).

3. Results

The initial total number of ICU admissions in our study time period was 116,410. After excluding patients with multiple admissions, incomplete data and those without research authorization, the final number of patients that was included in our cohort was 68,558. The details are shown in Supplemental Fig. e-1.

ABF was present in 30,610 (44.6%) patients. Patients with ABF had only an abnormal CAM-ICU score in 1985 (6.5%) patients, only an abnormal GCS/FOUR score in 18,323 (59.9%) patients, and abnormalities in CAM-ICU and GCS/FOUR in 10,302 (33.6%) during the same admission. The details of the demographics, predisposing conditions, ICU status and outcomes are shown in Table 1.

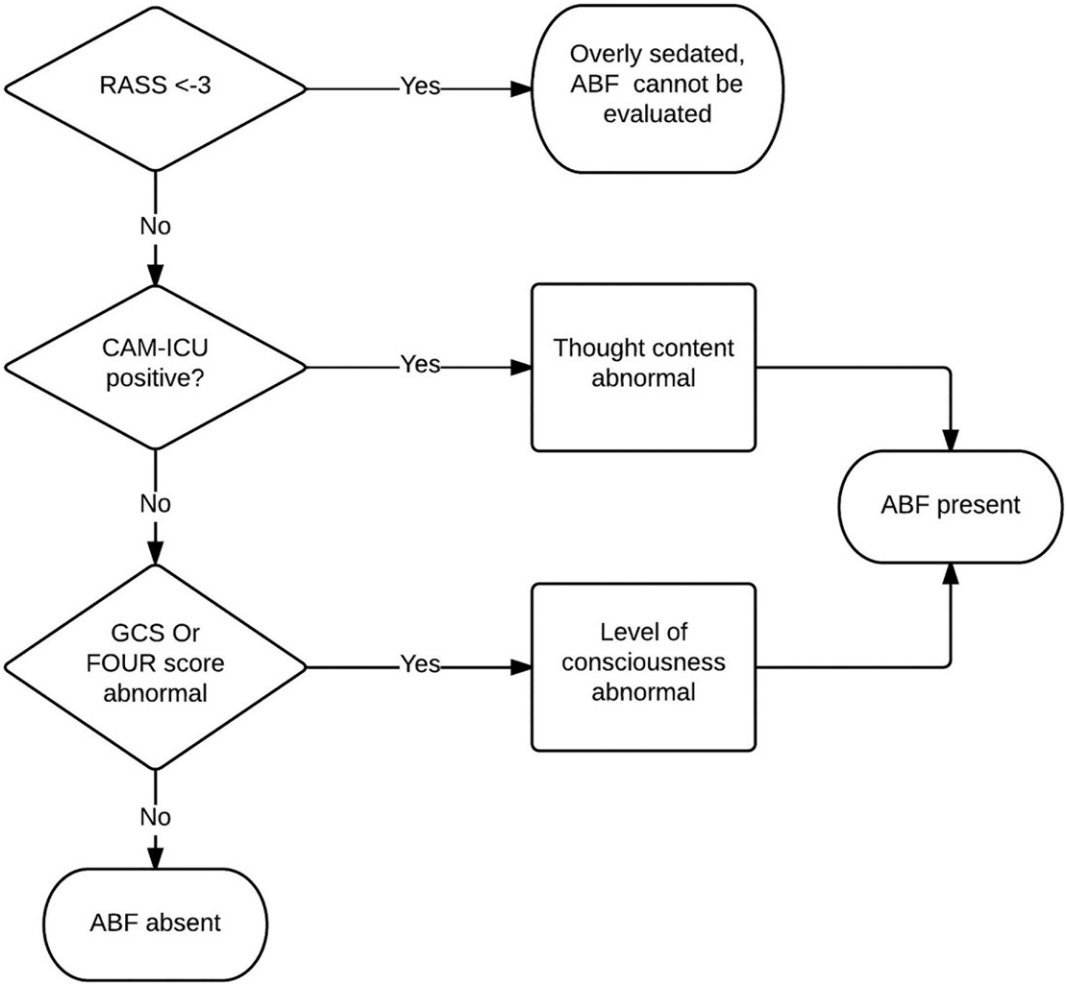

Fig. 1. Algorithm that was used to identify ABF in our study cohort. Abnormal GCS scores were <15 in non-ventilated patients, or <11 in ventilated patients. Abnormal FOUR scores were <16 in non-ventilated patients, and <13 in ventilated patients.

Table 1
Characteristics of patients who did and did not develop Acute Brain Failure (ABF).

Variables	ABF absent (37,948)	ABF present (30,610)	*p*-Value
Demographics			
Age	62 (49–73)	65 (52–77)	<0.001
Males	22,059 (58.1)	16,891 (55.2)	<0.001
BMI	28.3 (24.6–32.9)	27.7 (24.0–32.4)	<0.001
Predisposing conditions			
Hypertension	15,722 (41.4)	12,561 (41.0)	0.296
Myocardial infarction	2757 (7.3)	2352 (7.7)	0.038
Congestive heart failure	1985 (5.2)	2026 (6.6)	<0.001
Peripheral vascular disease	1146 (3.0)	1106 (3.6)	<0.001
Dementia	79 (0.2)	457 (1.5)	<0.001
Cerebrovascular accident	2210 (5.8)	2346 (7.7)	<0.001
Hemiplegia/paraplegia	103 (0.3)	116 (0.4)	0.014
Asthma	2473 (6.5)	1803 (5.9)	<0.001
COPD	4184 (11.0)	4615 (15.1)	<0.001
DM	5813 (15.3)	5051 (16.5)	<0.001
DM with complications	1243 (3.3)	1179 (3.9)	<0.001
Peptic ulcer	361 (0.9)	336 (1.1)	0.058
Moderate/severe liver disease	206 (0.5)	331 (1.1)	<0.001
Cirrhosis	622 (1.6)	872 (2.9)	<0.001
Renal failure	3079 (8.1)	2926 (9.6)	<0.001
Malignancy	6920 (16.6)	5299 (17.3)	0.011
Metastatic malignancy	1319 (3.5)	1048 (3.4)	0.710
Emergent surgery	254 (0.7)	353 (1.2)	<0.001
Charlson comorbidity index	4 (1–6)	4 (2–6)	<0.001
APACHE 3 at admission	49 (37–63)	62 (46–79)	<0.001
SOFA day 1	2 (1–5)	5 (3–7.8)	<0.001
Invasive ventilation	9168 (25.1)	15,220 (50.2)	<0.001
Vent days	0.3 (0.2–0.5)	0.8 (0.4–2.7)	<0.001
ICU length of stay	1.0 (0.8–1.7)	1.8 (0.9–3.8)	<0.001
ICU mortality	451 (1.2)	1203 (3.9)	<0.001
Hospital length of stay	4.4 (2.7–7.1)	7.6 (4.6–13.7)	<0.001
Hospital mortality	721 (2.0)	2494 (8.2)	<0.001

Data is presented as number (percentage) and median (interquartile range).

Table 2
Characteristics of the patients who developed delirium only, GCS/FOUR score abnormalities only and ABF.

	Delirium only[a] (1985)[b]	GCS/FOUR abnormal only[a] (18,323)[b]	ABF[a] (30,610)[b]
Age	67 (54–78)	63 (50–75)	65 (52–77)
Males	1112 (56.0)	9941 (54.3)	16,891 (55.2)
BMI	27.7 (24.0–32.1)	27.9 (24.2–32.6)	27.7 (24.0–32.4)
Hypertension	945 (47.6)	7194 (39.3)	12,561 (41.0)
Myocardial infarction	189 (9.5)	1285 (7.0)	2352 (7.7)
Congestive heart failure	128 (6.5)	1072 (5.9)	2026 (6.6)
Peripheral vascular disease	80 (4.0)	547 (3.0)	1106 (3.6)
Dementia	21 (1.1)	145 (0.8)	457 (1.5)
Cerebrovascular accident	166 (8.4)	1220 (6.7)	2346 (7.7)
Hemiplegia/paraplegia	5 (0.3)	58 (0.3)	116 (0.4)
Asthma	130 (6.6)	1121 (6.1)	1803 (5.9)
COPD	289 (14.6)	2396 (13.1)	4615 (15.1)
DM	387 (19.5)	2820 (15.4)	5051 (16.5)
DM with complications	91 (4.6)	608 (3.3)	1179 (3.9)
Peptic ulcer	36 (1.8)	169 (0.9)	336 (1.1)
Moderate/severe liver disease	30 (1.5)	162 (0.9)	331 (1.1)
Cirrhosis	77 (3.9)	439 (2.4)	872 (2.9)
Renal failure	217 (10.9)	1559 (8.5)	2926 (9.6)
Malignancy	413 (20.8)	3059 (16.7)	5299 (17.3)
Metastatic malignancy	108 (5.4)	577 (3.2)	1048 (3.4)
Emergent surgery	18 (0.9)	163 (0.9)	353 (1.2)
Charlson comorbidity index	5 (3–7)	4 (2–6)	4 (2–6)
APACHE 3 at admission	61 (47–76)	57 (42–73)	62 (46–79)
SOFA day 1	4 (2–6)	5 (2–7)	5 (3–7.8)
Invasive ventilation	606 (30.5)	8967 (49.4)	15,220 (50.2)
Vent days	0.4 (0.2–0.9)	0.6 (0.3–1.4)	0.8 (0.4–2.7)
ICU length of stay	1.2 (0.9–2.1)	1.2 (0.9–2.7)	1.8 (0.9–3.8)
ICU mortality	88 (4.4)	538 (3.0)	1203 (4.0)
Hospital length of stay	7.3 (4.7–12.4)	6.2 (4.1–9.8)	7.6 (4.6–13.7)
Hospital mortality	177 (8.9)	956 (5.3)	2494 (8.2)

[a] The three categories mentioned here i.e. delirium, GCS/FOUR score and ABF are not mutually exclusive and there is overlap in patients having either delirium, GCS/FOUR abnormalities or both.
[b] Data is presented as number (percentage) and median (interquartile range).

The ICU mortality of patients with delirium only, abnormal GCS/FOUR only and ABF was 4.4%, 3.0% and 4.0% while their hospital mortality was 8.9%, 5.3% and 8.2% (Table 2). The AUROC for prediction of ICU mortality were 0.613 (95% CI, 0.601–0.625) for delirium only, 0.618 (95% CI, 0.606–0.629) for abnormal GCS/FOUR only, and 0.640 (95% CI, 0.629–0.651) for ABF. Similarly, ABF discriminated better the patients who died in the hospital [AUROC 0.656 (95% CI, 0.647–0.664) for delirium only, 0.650 (95% CI, 0.641–0.658) for abnormal GCS/FOUR only, and 0.669 (95% CI, 0.662–0.677) for ABF] and was more predictive of ICU length of stay (r-squares 11.4% for delirium only, 6.4% for abnormal GCS/FOUR only, and 13.1% for ABF) and hospital length of stay (r-squares 9.8% for delirium only, 6.7% for abnormal GCS/FOUR only, and 12.0% for ABF).

Compared to patients with no ABF, patients with ABF had higher hospital mortality rates at discharge (OR 3.47; 95% CI 3.19–3.79), 90 days (OR 3.07; 95% CI 2.83–3.3) and 1 year (OR 2.36; 95% CI 2.24–2.50) after controlling for CCI and admission APACHE III scores ($p < 0.001$ in all cases). The Kaplan Meyer curves for survival in patients with and without ABF are shown in Fig. 2.

We evaluated all possible combinations of the different components of ABF (including the separate analysis of ventilated and non-ventilated patients) to come up with a severity score that would correlate with ICU and hospital mortality. 386 patients who had been diagnosed with ABF solely on the basis of abnormal FOUR score were excluded from the severity analyses because FOUR score was not consistently measured in all the ICUs before 2010. Thus, final analyses included 67,333 patients. The best discrimination was achieved with a GCS sum score of 8. Using this cut-off, the AUROCs for ICU and hospital mortality were 0.57 (95% CI, 0.56, 0.58) and 0.57 (95% CI, 0.57, 0.58), respectively. When this grading was applied to our cohort, 37,109 (55.1%) had no ABF (Grade 0), 25,283 (37.6%) had ABF Grade I and 4941 (7.3%) had ABF Grade II. The details of the demographics, predisposing conditions, and outcomes by ABF severity are presented in Table 3. ICU and hospital lengths of stay and ICU and hospital mortality rates increased from ABF grade 0 to grade I and from grade I to grade II. The Kaplan Meyer curves for survival by different grades of ABF are shown in Supplemental Fig. e-2.

Factors associated with the development of ABF on multivariable analysis were older age, female sex, invasive ventilation use, presence of moderate/severe liver disease, cirrhosis, renal failure, malignancy and COPD (Table 4). The neurologic conditions associated with ABF

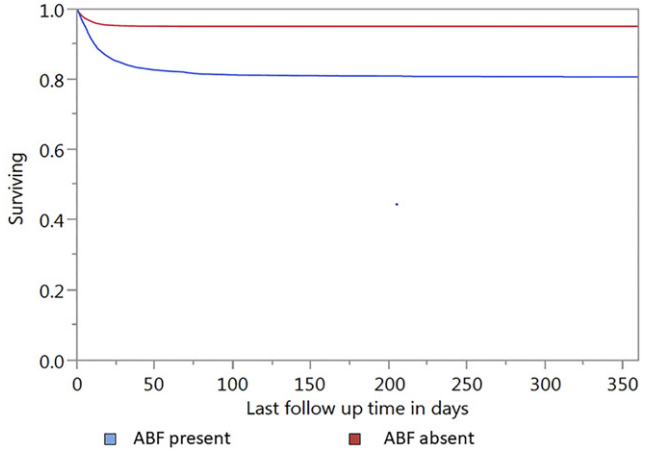

Fig. 2. The Kaplan Meyer curves for survival in patients with and without ABF.

Table 3
Comparison of the different grades of ABF.

Variables	Grade 0 ABF (37,109)	Grade I ABF (25,283)	Grade II ABF (4941)	*p*-Value
Age	62 (49–73)	66 (52–77)	63 (50–74)	<0.001
Males	21,582 (58.2)	13,694 (54.2)	2969 (60.1)	<0.001
BMI	28.3 (24.6–32.9)	27.7 (23.9–32.3)	27.9 (24.3–32.8)	<0.001
Hypertension	15,658 (42.2)	10,731 (42.4)	1806 (36.6)	<0.001
Myocardial infarction	2745 (7.4)	2010 (8.0)	339 (6.9)	0.006
Congestive heart failure	1981 (5.3)	1745 (6.9)	278 (5.6)	<0.001
Peripheral vascular disease	1142 (3.1)	963 (3.8)	140 (2.8)	<0.001
Dementia	78 (0.2)	414 (1.6)	43 (0.9)	<0.001
Cerebrovascular accident	2201 (5.9)	2023 (8.0)	319 (6.5)	<0.001
Hemiplegia/paraplegia	103 (0.3)	100 (0.4)	16 (7.3)	0.042
Asthma	2465 (6.6)	1558 (6.2)	240 (4.9)	<0.001
COPD	4166 (11.2)	3880 (15.4)	725 (14.7)	<0.001
DM	5782 (15.6)	4275 (16.9)	756 (15.3)	<0.001
DM with complications	1243 (3.3)	1029 (4.1)	145 (6.0)	<0.001
Peptic ulcer	361 (1.0)	294 (1.2)	42 (0.9)	<0.001
Moderate/severe liver disease	200 (0.5)	266 (1.1)	61 (11.6)	<0.001
Cirrhosis	611 (1.7)	710 (2.8)	157 (3.2)	<0.001
Renal failure	3058 (8.2)	2508 (9.9)	408 (8.3)	<0.001
Malignancy	6248 (16.8)	4611 (18.2)	678 (13.7)	<0.001
Metastatic malignancy	1311 (3.5)	931 (3.7)	116 (2.4)	<0.001
Charlson comorbidity index	4 (2–6)	5 (3–7)	4 (2–6)	<0.001
APACHE 3	49 (37–63)	61 (45–77)	71 (54–91)	<0.001
SOFA day 1	2 (1–5)	5 (2–7)	7 (5–9)	<0.001
Emergent surgery	235 (0.6)	255 (1.0)	83 (1.7)	<0.001
Invasive ventilation	9020 (25.3)	10,922 (43.7)	4058 (82.5)	<0.001
Vent days	0.3 (0.2–0.5)	0.7 (0.3–1.9)	1.8 (0.5–6.3)	<0.001
ICU length of stay	1.0 (0.8–1.7)	1.6 (1.0–3.1)	3.1 (1.2–8.8)	<0.001
ICU mortality	419 (1.2)	680 (2.7)	488 (9.9)	<0.001
Hospital length of stay	4.5 (2.5–7.1)	7.2 (4.4–12.3)	11.3 (6.2–23.0)	<0.001
Hospital mortality	677 (1.9)	1551 (6.2)	890 (18.1)	<0.001

Data is presented as number (percentage) and median (interquartile range).

were pre-existent dementia, stroke, and presence of hemiplegia/paraplegia. Hypertension was associated with a decreased frequency of ABF.

4. Discussion

The results of this large retrospective observational cohort study show that ABF has a high incidence in critically ill patients. ABF is associated with poor clinical outcomes including short and long term mortality. Moreover, as the severity of ABF increases, clinical outcomes worsen accordingly. Isolated impairment in the content of consciousness (i.e. delirium) was rare. Pre-existent dementia and requirement of invasive ventilation were the factors most strongly associated with ABF in this cohort. Other predisposing factors for ABF included older age, female sex, stroke, COPD, DM with complications, malignancy, moderate/severe liver disease, hemiplegia/paraplegia, and renal failure.

Table 4
Multivariate analyses for the factors predicting ABF.

Variable	OR (95% CI)	*p*-Value
Age (Unit OR)	1.009 (1.008–1.010)	<0.001
Males	0.83 (0.80–0.86)	<0.001
Invasive ventilation use	2.32 (2.24–2.40)	<0.001
Dementia	7.86 (6.15–10.19)	<0.001
Stroke	1.27 (1.19–1.36)	<0.001
COPD	1.25 (1.19–1.31)	<0.001
DM with complications	1.17 (1.07–1.29)	<0.001
Malignancy	1.14 (1.09–1.19)	<0.001
Moderate/severe liver disease	1.27 (1.00–1.60)	<0.001
Cirrhosis	1.47 (1.28–1.69)	<0.001
Hypertension	0.84 (0.81–0.87)	<0.001
Hemiplegia/paraplegia	1.49 (1.11–2.01)	0.008
Renal failure	1.09 (1.02–1.16)	0.007
Emergent surgery	1.32 (1.09–1.59)	0.004
ICU length of stay (Unit OR)	1.383 (1.368–1.398)	<0.001

Only variables with positive association have been listed in this table. Variables which were included in the multivariate analyses and were not shown to be associated with the development of ABF were: BMI, myocardial infarction, congestive heart failure, peripheral vascular disease, asthma, diabetes mellitus without complications, peptic ulcer and metastatic malignancy.

Critically ill patients often have alterations in the level and the content of consciousness. But, in most previous research and in practice, alterations in consciousness have been generally characterized using the concept of delirium. However, delirium does not include pronounced impairment in the level of alertness and assessing the RASS score for excessive sedation is necessary before checking for delirium. Studies conducted by Haenggi et al. have shown that the proportion of CAM-ICU-positive evaluations decreased from 53% to 31% ($p < 0.001$) after excluding the sedated patients using RASS [26]. If the RASS score is between −3 to −5, evaluation of delirium is not possible because its assessment depends on the ability of the patient to interact at least to some degree with the examiner. However, many previous studies assessing delirium do not report the use of the RASS score or exclude excessive sedation [5,27,28]. Therefore, some patients in these studies could have still been sedated during cognitive evaluation and might have been falsely categorized as delirious. Also, previous studies incorporating an evaluation of the level of consciousness have characteristically restricted it to the presence or absence of coma; yet, critically ill patients can have alterations in the level of consciousness without being comatose as contemplated in our definition of ABF.

We found a hospital mortality rate of 8.2% among patients with ABF. This is similar to the mortality seen with delirium in a meta-analysis by Cole et al. that found 14.2% of delirious patients died during one month of the ICU admission. However, ABF identifies a nearly 60% more at-risk patients than delirium alone, expanding our ability to detect patients at risk for neurologic damage. In our models, ABF was also superior to delirium only or abnormal level of consciousness only for the prediction of ICU and hospital mortality and ICU and hospital length of stay.

The variables associated with ABF in our multivariable analysis have been previously associated with delirium in other studies. Previous studies have indicated that dementia, respiratory disease and age are the strongest predisposing risk factors for delirium and have also found associations between delirium and mechanical ventilation, APACHE score, metabolic acidosis, and alcohol abuse [29,30]. Results from our study, as well as results from a study conducted by Krzych et al., showed that patients with hypertension were less likely to develop delirium [31]. However, other studies have suggested that hypertension may actually be a risk factor for the development of delirium in the ICU [29,30,32]. Thus, the relationship between blood pressure and ABF needs further investigation.

This study has several strengths. The large size of our cohort (68,558 unique ICU admissions) gave us ample statistical power. Meanwhile, the combination of medical and surgical patients increases the generalizability of our findings. All the data elements included in our analysis were gathered automatically from the digital records using previously validated data collection tools [19,22-24]. This automation can be easily replicated at other institutions and allows for large scale data retrieval with a significant reduction in the likelihood of manual errors, both at the time of initial variable measurement and at the time of data retrieval. Because of the reliability of charted elements, ABF can help identify hospital exposures of interest and design and test preventative quality improvement and research strategies.

Our study also has several limitations. First, although we took precautions to try to minimize the confounding effect of sedation, it is still possible that sedation may have contaminated our assessments. Unlike ours, previous studies have not consistently excluded CAM-ICU evaluations in patients with RASS of −3 to −5. Yet, even milder degrees of sedation can result in a positive CAM-ICU and a potentially erroneous diagnosis of delirium. Second, we excluded patients from the Neurosciences ICU and the Pediatric ICUs. This was intentional to avoid the

inclusion of patients with acute cerebral disease upon admission and to focus on adult patients, but this limits the generalizability of our findings to these populations. Third, because ours is a tertiary referral center, referral bias cannot be excluded. We used RASS scores to identify which patients were appropriate for delirium screening as recommended by the investigators who developed the CAM-ICU score. We are convinced that this is a necessary step before evaluating patients with the CAM-ICU score to screen for delirium. Yet, this practice is not universal, which may affect the generalizability of our findings to other settings. In this analysis we did not incorporate a detailed evaluation of drugs, metabolic factors and other in-hospital variables on the development of ABF. We are currently evaluating these in-hospital factors and the results of this analysis will be reported in a separate study. Lastly the length of stay and outcomes could be confounded by the presence of death.

5. Conclusions

We conclude that ABF reliably identifies patients with critical illness who develop acute cerebral dysfunction with disturbance in the content or level of consciousness. ABF is more common in older patients with greater acute disease severity and extensive comorbidities and its development is associated with worse short- and long-term prognosis. Further research is necessary to identify modifiable risk factors for ABF.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2017.08.028.

References

[1] Diagnostic and Statistical Manual of Mental Disorders V5th ed. Washington DC: American Psychiatric Association; 2013.
[2] Cavallazzi R, Saad M, Marik PE. Delirium in the ICU: an overview. Ann Intensive Care 2012;2(1):49.
[3] Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29(7):1370–9.
[4] Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369(14):1306–16.
[5] Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Elseviers M, Bossaert L. A comparison of the CAM-ICU and the NEECHAM Confusion Scale in intensive care delirium assessment: an observational study in non-intubated patients. Crit Care 2008;12(1):R16.
[6] Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell Jr FE, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291(14):1753–62.
[7] Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med 2010;38(7):1513–20.
[8] Lat I, McMillian W, Taylor S, Janzen JM, Papadopoulos S, Korth L, et al. The impact of delirium on clinical outcomes in mechanically ventilated surgical and trauma patients. Crit Care Med 2009;37(6):1898–905.
[9] Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW, et al. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med 2010;38(12):2311–8.
[10] van den Boogaard M, Schoonhoven L, Evers AW, van der Hoeven JG, van Achterberg T, Pickkers P. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. Crit Care Med 2012;40(1):112–8.
[11] Pompei P, Foreman M, Rudberg MA, Inouye SK, Braund V, Cassel CK. Delirium in hospitalized older persons: outcomes and predictors. J Am Geriatr Soc 1994;42(8):809–15.
[12] Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med 2009;180(11):1092–7.
[13] Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. Crit Care 2008;12:S3 Suppl. 3.
[14] Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014;383(9920):911–22.
[15] Kalabalik J, Brunetti L, El-Srougy R. Intensive care unit delirium: a review of the literature. J Pharm Pract 2014;27(2):195–207.
[16] McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: occurrence and clinical course in older patients. J Am Geriatr Soc 2003;51(5):591–8.
[17] European Delirium A, American Delirium S. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. BMC Med 2014;12:141.
[18] Reddy DRS, Singh TD, Guru PK, Sakusic A, Gajic O, O'Horo JC, et al. Identification of acute brain failure using electronic medical records. J Crit Care 2016;34:12–6.
[19] Herasevich V, Pickering BW, Dong Y, Peters SG, Gajic O. Informatics infrastructure for syndrome surveillance, decision support, reporting, and modeling of critical illness. Mayo Clin Proc 2010;85(3):247–54.
[20] Alsara A, Warner DO, Li G, Herasevich V, Gajic O, Kor DJ. Derivation and validation of automated electronic search strategies to identify pertinent risk factors for postoperative acute lung injury. Mayo Clin Proc 2011;86(5):382–8.
[21] Herasevich V, Kor DJ, Li M, Pickering BW. ICU data mart: a non-iT approach. A team of clinicians, researchers and informatics personnel at the Mayo Clinic have taken a homegrown approach to building an ICU data mart. Healthc Inform 2011;28(11)[42, 4-5].
[22] Larson KJ, Hamlin RJ, Sprung J, Schroeder DR, Weingarten TN. Associations between Charlson Comorbidity Index and surgical risk severity and the surgical outcomes in advanced-age patients. Am Surg 2014;80(6):555–60.
[23] Harrison AM, Yadav H, Pickering BW, Cartin-Ceba R, Herasevich V. Validation of computerized automatic calculation of the sequential organ failure assessment score. Crit Care Res Prac 2013;2013:975672.
[24] Keegan MT, Whalen FX, Brown DR, Roy TK, Afessa B. Acute Physiology and Chronic Health Evaluation (APACHE) III outcome prediction after major vascular surgery. J Cardiothorac Vasc Anesth 2008;22(5):713–8.
[25] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44(3):837–45.
[26] Haenggi MBS, Brechbuehl R, Brunello A, Jakob SM, Takala J. Effect of sedation level on the prevalence of delirium when assessed with CAM-ICU and ICDSC. Intensive Care Med 2013;39(12):2171–9.
[27] Balas MC, Happ MB, Yang W, Chelluri L, Richmond T. Outcomes associated with delirium in older patients in surgical ICUs. Chest 2009;135(1):18–25.
[28] Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286(21):2703–10.
[29] Zaal IJDJWPD, Peelen LM, Slooter AJ. A systematic review of risk factors for delirium in the ICU. Crit Care Med 2015;43:1.
[30] Rompaey BV, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L. Risk factors for intensive care delirium: a systematic review. Intensive Crit Care Nurs 2008;24:98–107.
[31] Krzych LJ, Wybraniec MT, Krupka-Matuszczyk I, Skrzypek M, Bolkowska A, Wilczynski M, et al. Complex assessment of the incidence and risk factors of delirium in a large cohort of cardiac surgery patients: a single-center 6-year experience. Biomed Res Int 2013;2013:835850.
[32] Huai JYX. A meta-ananlysis of critically ill patients reveals several potential risk factors for delirium. Gen Hosp Psychiatry 2014;36:488–96.