Brief Report

Association of Persistent Intense Thirst With Delirium Among Critically Ill Patients: A Cross-sectional Study

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Abstract

Context. Thirst is a prevalent distressing symptom often reported by patients in the intensive care unit (ICU). Little is known about the association of thirst with delirium.

Objective. We aimed to investigate the relationship between thirst and delirium.

Methods. This retrospective cross-sectional study enrolled 401 patients who were evaluated for thirst intensity in the ICU between March 2017 and October 2017. We assessed thirst intensity on a scale of 0−10 (with 10 being the worst) and defined intense thirst as a score ≥8. If intense thirst persisted for more than 24 hours, we defined it as persistent intense thirst. Delirium was screened using the Intensive Care Delirium Screening Checklist. Propensity score matching and inverse probability of treatment weighting analyses were performed.

Results. Of 401 patients, 66 (16.5%) had intense thirst sensation for more than 24 hours. After matching, patients with persistent intense thirst showed an increased risk for delirium compared with those without persistent intense thirst (odds ratio, 4.95; 95% confidence interval, 2.58−9.48; $P < 0.001$). Propensity score weighted logistic regression analysis also indicated that persistent intense thirst was significantly associated with delirium (odds ratio, 5.74; 95% confidence interval, 2.53−12.99; $P < 0.001$).

Conclusion. Intense thirst persisting for more than 24 hours was associated with increased risk for delirium. J Pain Symptom Manage 2019;57:1114−1120.

Key Words

Thirst, delirium, critically ill

Background

The sensation of thirst results in a complex physiological drive to drink. Critically ill patients often experience distressful episodes of intense thirst during their stay in the intensive care unit (ICU). In an assessment of 10 symptoms, thirst was regarded as having the greatest intensity according to 70.8% of 171 patients in the ICU, and it was the second most prevalent symptom.[1] Despite its wide prevalence, thirst remains underestimated and undertreated.[2] Thirst can be stimulated by either increased plasma osmolarity (osmotic thirst) or marked decreases in plasma volume (hypovolemic thirst). Central osmoreceptor neurons stimulate the release of arginine vasopressin peptide, and the low volume and pressure sensors in the kidneys increase circulating renin-angiotensin levels. The released angiotensin II promotes aldosterone secretion to retain sodium and water. Acting in harmony, these central and peripheral signals activate specific sites in the brain to stimulate the conscious perception of thirst.[3]

Neuroimaging studies have shown that the anatomic origin of thirst is in the anterior wall of the third ventricle, anterior cingulate, parahippocampal gyrus, insula, and cerebellum. These brain regions are also associated with complex functions, including emotional behavior and thought.[4]

Delirium is defined as the acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or an altered consciousness level.[5] Previous

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studies have focused on the deleterious effects of delirium on the prognosis of ICU patients.[6,7] Preventing, detecting, and treating delirium have become one of the most important challenges for critical care providers. Adequate pain management and promoting sleep-wake cycles are key to effectively treating patients at high risk for delirium in the ICU setting.[5,8] It is also important that any other sources of stress experienced by patients should be assessed and managed appropriately.

Over the past decade, there have been several studies regarding risk factors for delirium as well as pharmacological and nonpharmacological interventions to prevent delirium. However, little is known about the association between thirst and delirium. We hypothesized that patients experiencing intense thirst have a significant risk for delirium. In this study, we aimed to determine whether persistent intense thirst is strongly associated with delirium development.

Methods

Study Design and Participants

This study was approved by the ethics committee of our institution (approval number 2018−70). This single-center retrospective cross-sectional study reviewed data obtained from our institutional database from March 2017 to October 2017. The participating institution had 22 mixed medical-surgical ICU beds and a closed ICU system. We retrospectively identified adult patients (aged ≥18 years) who were examined for thirst intensity during their ICU stay. In our institution, patients were routinely asked to report about their thirst at least twice a day. We began to assess thirst intensity from their first ICU day. Thirst intensity was assessed using the numeric rating scale (NRS) of 0−10.[2,9,10] Anchor words for thirst intensity were "no thirst" = 0 and "worst possible thirst" = 10. Self-report with NRS was used because it is the gold standard for symptom assessment. Validity of the NRS has been established.[11,12] Orientation was confirmed if it was between −1 and +1 on the Richmond Agitation-Sedation Scale before thirst evaluation. When patients were deeply sedated or could not express their sensation, we scored it as "unmeasurable." We reassessed thirst intensity on the next day in such cases and continued this process until the time of ICU discharge. We excluded patients whose thirst intensity score was incomplete or remained unmeasurable until ICU discharge. We also excluded patients who underwent surgery of the oral cavity because it could affect the thirst sensation.

Definition of Persistent Intense Thirst

We defined intense thirst as a score ≥8, based on a previous study.[13] If intense thirst persisted for more than 24 hours, we defined it as persistent intense thirst.

Thirst was managed by primary nurses, and the management comprised providing ice and ice-cold water sprays, application of lip and oral moisturizers, and maintaining appropriate fluid volume.

Data Collection

Demographic and clinical characteristics of patients, including age, sex, body mass index, history of dementia, laboratory values, medications (opioids and dexmedetomidine), first 24-hour Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score, mechanical ventilation, continuous renal replacement therapy (CRRT), and presence of delirium, were extracted. Data on laboratory values were also extracted when the patient's thirst intensity was at the maximal value.

Outcomes

The primary clinical outcome was delirium during ICU stay, which was assessed using the Intensive Care Delirium Screening Checklist. The Intensive Care Delirium Screening Checklist, including the Japanese version, is a valid, reliable, and feasible tool for detecting delirium in ICU patients; a score ≥4 was defined as clinical delirium.[5,14,15]

Statistical Analysis

We divided the patients into two groups based on their thirst intensity score: persistent intense thirst group and without persistent intense thirst group. The two-sample t-test or Wilcoxon rank-sum test was used, as appropriate, to compare continuous variables. For categorical variables, the chi-square test or Fisher's exact test was used. A propensity score (PS) matching analysis was performed to reduce the effects of selection bias and potential confounders between each group. PS was calculated based on a logistic regression model with potential confounding variables (age, sex, body mass index, APACHE II score, SOFA score, type of admission [surgical or medical], neurological disease, blood urea nitrogen, sodium, plasma osmolarity, dementia, diabetes mellitus, dexmedetomidine use, benzodiazepine use, calcium antagonist use, opioid use, mechanical ventilation, and CRRT) using clinical knowledge. Two groups were matched based on 1:4 nearest neighbors matching method. A PS difference of 0.15 was adopted as the maximum caliper width for matching. The standardized difference test was used to measure covariate balance. Logistic regression was used to evaluate the association between persistent intense thirst and delirium in matched groups. In addition, the inverse probability of treatment weighting (IPTW) analysis was performed to evaluate the

sensitivity of the results by estimating propensity scores used to weigh individual observations. The IPTW analysis adjusts the confounding factor and has the advantage of evaluating causal effects without reducing sample size. All *P*-values were two-tailed, and $P < 0.05$ was considered statistically significant. We used STATA 14.2 (StataCorp, College Station, TX) and R statistical software (version 3.5.0; R Foundation for Statistical Computing, Vienna, Austria) for the analysis. Our missing values were handled using complete-case analysis.

Results

This study enrolled 401 patients. Figure 1 shows the patient flow diagram. A total of 163 patients (40.6%) experienced intense thirst during their ICU stay, and 66 (16.5%) had sensation of intense thirst for more than 24 hours (persistent intense thirst). An episode of delirium occurred in 47 (11.7%) of the 401 patients. The baseline characteristics of patients are presented in Table 1. Before the matching, APACHE II and SOFA scores, blood urea nitrogen, sodium, and plasma osmolarity were significantly higher in the persistent intense thirst group than in the without persistent intense thirst group. Dexmedetomidine, opioid, and calcium antagonists were the drugs more frequently used by patients with persistent intense thirst than by those without persistent intense thirst. Moreover, a greater proportion of patients with mechanical ventilation and CRRT were observed in the persistent intense thirst group than in the without persistent intense thirst group.

PS was estimated using logistic regression models with potential confounders, which had c-statistics of 0.80. According to PS, 65 patients with persistent intense thirst were matched with 261 patients without persistent intense thirst. The absolute standardized differences in the covariates between groups were improved after matching (Table 1). In the logistic regression model, patients with persistent intense thirst showed an increased risk for delirium than did patients without persistent intense thirst (odds ratio, 4.95; 95% confidence interval, 2.58−9.48; $P < 0.001$) (Table 2). In the IPTW analysis, the absolute standardized differences in the covariates were controlled well (Fig. 2). Persistent intense thirst was also significantly associated with delirium (odds ratio, 5.74; 95% confidence interval, 2.53−12.99; $P < 0.001$) (Table 2).

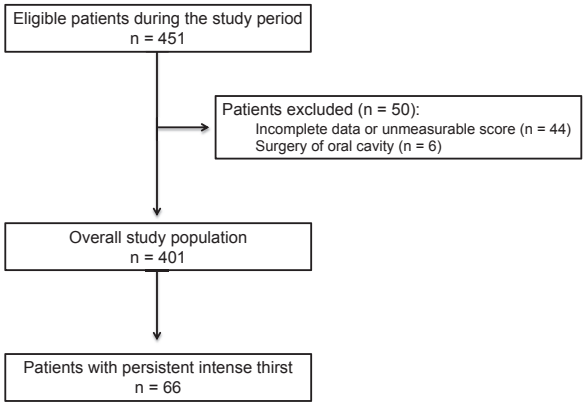

Fig. 1. Flow diagram of patients in the study.

Discussion

In this study, we demonstrated that among patients who could report their sensation of thirst, approximately 40% of patients complained of a strong sensation of thirst during their ICU stay. If intense thirst did not resolve and persisted for more than 24 hours, it was significantly related to delirium. To our knowledge, this is the first study to reveal the association between thirst sensation and delirium among ICU patients.

The interaction of pain and delirium is well known.[8] For management of delirium, it is necessary to control pain appropriately, which is one of the most distressing symptoms in the ICU.[16,17] Thirst is a common complaint and a source of distress for many critically ill patients. Like pain, this unpleasant symptom may cause frustration, anger, anxiety, and agitation, which are associated with delirium onset. In addition, intense thirst, which possibly persists overnight, may interfere with sleep quality. Delirium prevention and treatment is essential to improve sleep quality,[16,17] and thirst was listed as one of physiologic factors disrupting sleep.[17] Moreover, thirst is induced by decreased plasma volume (hypovolemic thirst). Studies on elderly medical patients have consistently reported that dehydration is a risk factor for delirium.[18–21] The role of fluid deficit in the pathogenesis of delirium remains unclear; the possible explanations for this include tissue hypoperfusion (especially cerebral and renal), increased concentration of drugs (e.g., opioids) and/or their metabolites in a depleted intravascular volume, and decreased renal elimination of drugs (e.g., opioids) and/or metabolites.[21] Available evidence suggests that assisted fluid administration may help prevent and reduce delirium, although such evidence is based on studies in patients with cancer.[22,23]

Strong thirst sensation urges people to drink water, which can be an absolute solution. However, critical illness prevents patients from drinking as much water as they want. A nil per os status or fluid restriction is prevalent in the ICU. Optimal fluid management is one of the methods for alleviating thirst when oral intake is insufficient. Intensive care providers usually monitor cardiac output, filling pressure as well as urine output, and fluid balance to achieve goals of

Table 1
Basic Characteristics of Patients Before and After Matching'

	Before Matching ($n = 401$)				After Matching ($n = 326$)			
Baseline Characteristics	Persistent Intense Thirst ($n = 66$)	Without Persistent Intense Thirst ($n = 335$)	*P*-value	ASD	Persistent Intense Thirst ($n = 65$)	Without Persistent Intense Thirst ($n = 261$)	*P*-value	ASD
Age (years)	69.0 [61.3, 76.0]	68.0 [59.0, 75.0]	0.115	0.203	69.0 [61.0, 76.0]	67.0 [63.0, 76.0]	0.598	0.075
Males (%)	37 (56.1)	215 (64.2)	0.214	0.157	37 (56.9)	144 (55.2)	0.889	0.035
Body mass index	23.5 [21.0, 25.3]	22.1 [19.9, 24.4]	0.083	0.246	23.5 [21.0, 25.3]	22.6 [20.6, 25.1]	0.937	0.011
APACHE II score	14.5 [9.0, 21.8]	10.0 [7.0, 17.0]	<0.001	0.565	15.0 [9.0, 22.0]	16.0 [8.0, 22.0]	0.767	0.053
SOFA score	5.0 [3.0, 7.75]	3.0 [1.0, 6.0]	<0.001	0.647	5.0 [3.0, 8.0]	6.0 [2.0, 9.0]	0.983	0.04
Surgery (%)	50 (75.8)	286 (85.4)	0.067	0.226	50 (76.9)	213 (81.6)	0.385	0.115
Neurological disease (%)	2 (3.0)	23 (6.9)	0.401	0.185	2 (3.1)	9 (3.4)	1	0.021
Blood urea nitrogen (mg/dL)	22.0 [16.0, 35.8]	15 [11.0, 20.0]	<0.001	0.614	22.0 [16.0, 36.0]	19.0 [14.0, 31.0]	0.586	0.08
Sodium (mEq/L)	141.0 [138.0, 144.0]	140.0 [137.0, 142.0]	0.005	0.363	141.0 [138.0, 144.0]	141.0 [139.0, 143.0]	0.822	0.032
Plasma osmolarity (mOsm/L)	298.2 [293.7, 306.3]	293.7 [287.7, 298.8]	<0.001	0.613	298.1 [293.7, 306.4]	297.6 [292.2, 304.0]	0.807	0.037
Dementia (%)	9 (13.6)	24 (7.2)	0.090	0.174	8 (12.3)	24 (9.2)	0.485	0.1
Diabetes mellitus (%)	11 (16.7)	60 (17.9)	0.947	0.078	10 (15.4)	48 (18.4)	0.717	0.08
Dexmedetomidine use (%)	25 (37.9)	84 (25.1)	0.048	0.287	25 (38.5)	103 (39.5)	1	0.02
Benzodiazepine use (%)	4 (6.1)	10 (3.0)	0.261	0.145	4 (6.2)	16 (6.1)	1	0.001
Opioid use (%)	35 (53.0)	98 (29.3)	<0.001	0.507	34 (53.1)	126 (49.2)	0.675	0.078
Calcium antagonists use (%)	38 (57.6)	141 (42.1)	0.022	0.296	37 (56.9)	148 (56.7)	1	0.004
Mechanical ventilation (%)	41 (62.1)	135 (40.3)	0.002	0.478	40 (62.5)	164 (64.1)	0.885	0.032
CRRT (%)	16 (24.2)	23 (6.9)	<0.001	0.501	15 (23.4)	51 (19.9)	0.604	0.085

APACHE = Acute Physiology and Chronic Health Evaluation; ASD = absolute standardized difference; CRRT = continuous renal replacement therapy; SOFA = Sequential Organ Failure Assessment. Continuous variables are presented as medians [interquartile range].

Table 2
Odds Ratios of Persistent Intense Thirst for Delirium in Propensity Matching and IPTW Analyses'

Model	Odds Ratio (95% CI)	*P*-value
Unadjusted	7.75 (4.02–14.94)	<0.001
Propensity matching	4.95 (2.58–9.48)	<0.001
IPTW	5.74 (2.53–12.99)	<0.001

CI = confidence interval; IPTW = inverse probability of treatment weighting.

fluid therapy. However, integrating the entirety of information for optimal fluid management is complex in critically ill patients.[24] In addition, fluid-restrictive strategies are often used as a standard practice for special types of surgery or for patients with acute respiratory distress syndrome based on several studies that show an association between fluid overload and worse outcome.[25–31] Moreover, aggressive and active fluid removal through diuretics and renal replacement therapy is necessary in some cases to obtain consecutive negative fluid balance, which is also related to patient outcomes.[32] Stotts et al.[9] reported that a high dose of furosemide is an important predictor of thirst. These types of fluid management may put the patients at risk for relative volume losses.

Although dehydration (broadly defined as inadequate fluid intake) and hyperosmolar state have often been recognized as major stimuli of thirst, they have not been consistently correlated with patients' thirst reports. Several studies have failed to show an association between thirst and biochemical markers of fluid deficit or dehydration.[33–37] Morita et al.[13] identified specific conditions such as mouth breathing due to hypoxia and stomatitis as possible etiologies of thirst. Furthermore, common dipsogenic medications, such as opioids, serotonin reuptake inhibitors, antihypertensive drugs and proton pump inhibitors,[3,9] are frequently used in the ICU. Besides the optimal fluid therapy, switching opioids to nonopioids could be one of the options to palliate intense thirst sensation.[2] Moreover, thirst can be relieved by simple and inexpensive interventions, for example, oral swab wipes and sterile ice-cold water sprays.[10] However, further research is needed to confirm whether these aggressive thirst treatments have some beneficial effects on delirium prevention.

Our study has several potential limitations. First, our data showed associations rather than cause and effect because of the study's cross-sectional design. Further well-designed study is needed to clarify the association. Second, the sample size was relatively small because this study was conducted in a single center. Third, we did not assess patients' sleep quality, which is proposed to be strongly associated with delirium. Finally, the occurrence of delirium in this study was less frequent than that in other studies. To evaluate thirst intensity, patients needed to be able to communicate well because thirst intensity was based on self-report. Thirst intensity of patients with impaired communication, including those with advanced dementia or severe neurological disorders, which are possible risks of delirium, could not be assessed by self-report. Therefore, we could not include such patients in this study. Although our findings require further investigation, they contribute to existing knowledge on thirst

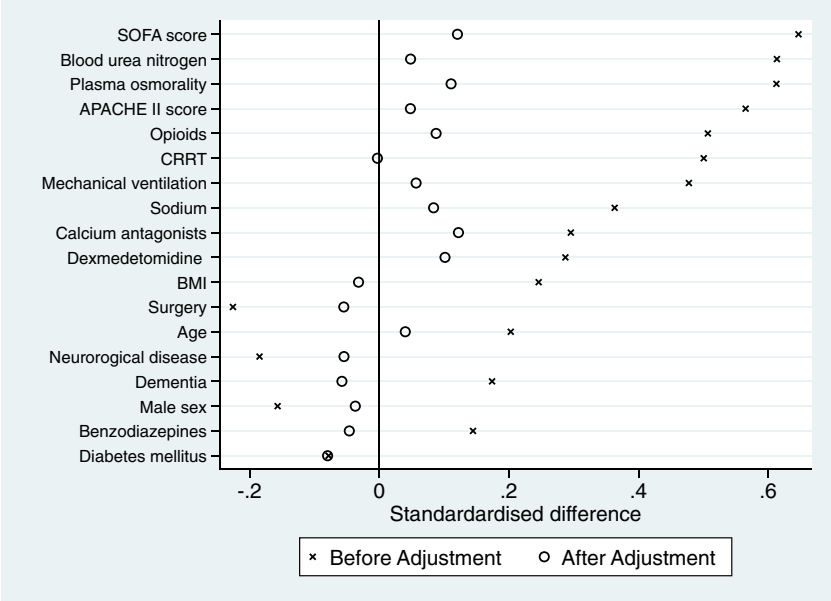

Fig. 2. Standardized differences of general characteristics before and after adjustment in the IPTW analysis. IPTW = inverse probability of treatment weighting; SOFA = Sequential Organ Failure Assessment; APACHE = Acute Physiology and Chronic Health Evaluation; CRRT = continuous renal replacement therapy; BMI = body mass index.

sensation, which is one of the most common distressing symptoms in the ICU.

Conclusions

Our study found that intense thirst sensation was prevalent in the ICU and that thirst persisting for more than 24 hours was significantly associated with increased risk for delirium. Therefore, critical care providers should assess and monitor patients' thirst intensity. Further study is required to examine whether alleviating the burden of thirst has an impact on patients at high risk for delirium.

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Availability of data and materials: Data analyzed in this study are available from the corresponding author upon reasonable request.

The authors declare no conflict of interest in relation to this study.

References

1. Puntillo KA, Arai S, Cohen NH, et al. Symptoms experienced by intensive care unit patients at high risk of dying. Crit Care Med 2010;38:2155–2160.

2. Chanques G, Nelson J, Puntillo K. Five patient symptoms that you should evaluate every day. Intensive Care Med 2015;41:1347–1350.

3. Arai S, Stotts N, Puntillo K. Thirst in critically ill patients: from physiology to sensation. Am J Crit Care 2013;22:328–335.

4. Danziger J, Zeidel ML. Osmotic homeostasis. Clin J Am Soc Nephrol 2015;10:852–862.

5. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263–306.

6. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753–1762.

7. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306–1316.

8. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. N Engl J Med 2014;370:444–454.

9. Stotts NA, Arai SR, Cooper BA, Nelson JE, Puntillo KA. Predictors of thirst in intensive care unit patients. J Pain Symptom Manage 2015;49:530–538.

10. Puntillo K, Arai SR, Cooper BA, Stotts NA, Nelson JE. A randomized clinical trial of an intervention to relieve thirst and dry mouth in intensive care unit patients. Intensive Care Med 2014;40:1295–1302.

11. Chanques G, Viel E, Constantin JM, et al. The measurement of pain in intensive care unit: comparison of 5 self-report intensity scales. Pain 2010;151:711–721.

12. Rahu MA, Grap MJ, Ferguson P, et al. Validity and sensitivity of 6 pain scales in critically ill, intubated adults. Am J Crit Care 2015;24:514–523.

13. Morita T, Tei Y, Tsunoda J, Inoue S, Chihara S. Determinants of the sensation of thirst in terminally ill cancer patients. Support Care Cancer 2001;9:177–186.

14. Ouimet S, Riker R, Bergeron N, et al. Subsyndromal delirium in the ICU: evidence for a disease spectrum. Intensive Care Med 2007;33:1007–1013.

15. Nishimura K, Yokoyama K, Yamauchi N, et al. Sensitivity and specificity of the Confusion assessment method for the intensive care Unit (CAM-ICU) and the intensive care delirium screening Checklist (ICDSC) for detecting post-cardiac surgery delirium: a single-center study in Japan. Heart Lung 2016;45:15–20.

16. Bush SH, Kanji S, Pereira JL, et al. Treating an established episode of delirium in palliative care: expert opinion and review of the current evidence base with recommendations for future development. J Pain Symptom Manage 2014;48:231–248.

17. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/Sedation, delirium, Immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018;46:e825–e873.

18. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990;263:1097–1101.

19. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 1993;119:474–481.

20. Seymour DG, Henschke PJ, Cape RD, Campbell AJ. Acute confusional states and dementia in the elderly: the role of dehydration/volume depletion, physical illness and age. Age Ageing 1980;9:137–146.

21. Lawlor PG. Delirium and dehydration: some fluid for thought? Support Care Cancer 2002;10:445–454.

22. Bruera E, Franco JJ, Maltoni M, Watanabe S, Suarez-Almazor M. Changing pattern of agitated impaired mental status in patients with advanced cancer: association with cognitive monitoring, hydration, and opioid rotation. J Pain Symptom Manage 1995;10:287–291.

23. Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. Arch Intern Med 2000;160:786–794.

24. Martin GS. State-of-the-art fluid management in critically ill patients. Curr Opin Crit Care 2014;20:359.

25. Vaara ST, Korhonen AM, Kaukonen KM, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care 2012;16:R197.

26. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2006;34:344–353.

27. Sakr Y, Rubatto Birri PN, Kotfis K, et al. Higher fluid balance increases the risk of Death from Sepsis: results from a Large International Audit. Crit Care Med 2017;45:386–394.

28. Jozwiak M, Silva S, Persichini R, et al. Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome. Crit Care Med 2013; 41:472–480.

29. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564–2575.

30. Ishikawa S, Griesdale DE, Lohser J. Acute kidney injury after lung resection surgery: incidence and perioperative risk factors. Anesth Analg 2012;114:1256–1262.

31. Lin CX, Guo Y, Lau WY, et al. Optimal central venous pressure during partial hepatectomy for hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2013;12:520–524.

32. Malbrain ML, Marik PE, Witters I, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther 2014;46:361–380.

33. Burge FI. Dehydration symptoms of palliative care cancer patients. J Pain Symptom Manage 1993;8:454–464.

34. Ellershaw JE, Sutcliffe JM, Saunders CM. Dehydration and the dying patient. J Pain Symptom Manage 1995;10: 192–197.

35. Gross CR, Lindquist RD, Woolley AC, et al. Clinical indicators of dehydration severity in elderly patients. J Emerg Med 1992;10:267–274.

36. Musgrave CF, Bartal N, Opstad J. The sensation of thirst in dying patients receiving i.v. hydration. J Palliat Care 1995; 11:17–21.

37. Shirreffs SM, Merson SJ, Fraser SM, Archer DT. The effects of fluid restriction on hydration status and subjective feelings in man. Br J Nutr 2004;91:951–958.