**The occurrence of fluid overload in critically ill patients admitted to the ICU: is action needed?**

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**Background**: Fluid infusion represents one of the cornerstones of Intensive care unit (ICU) therapies. However, ICU-acquired fluid overload (FO) as a consequence of excessive fluid administration is common and seems to be linked to worse long-term outcome[1-3]. Data on fluid prescription and FO occurrence in Dutch population is lacking, likewise the immediate effect of even moderate FO on patient's clinical state has been poorly described.

**Objectives:** In this study we aimed to shed some light on the current fluid management strategy in our hospital by quantifying the occurrence of moderate and severe FO during the first 5 days of ICU admission. In addition, we studied the effect of FO on mortality and mean SOFA score as a surrogate marker of organ dysfunction.

**Material and methods:** Retrospective study. All adult patients (> 18 years old) admitted to the ICU/MCU wards in Noordwest Ziekenhuisgroep Hospitals in North Holland, the Netherlands within the period of 1 September 2019 and 18 March 2020, were included. FO was calculated as follows: [Σ daily (fluid intake (L)-total output (L))/baseline bodyweight (in kilograms)] x 100 [3-4]. A cutoff value of 5% and 10% defined moderate and severe FO, respectively [5]. Univariate analysis was performed with Student's t and chi-square test, for continuous and categorical variables, respectively. A multivariate regression model was used to adjust the association between FO and the outcome variables mean SOFA score and 28-day mortality for confounding factors. Furthermore, to account for the longitudinal character of the daily SOFA scores an additional linear mixed model analysis was performed to compare the daily mean SOFA scores between the FO groups.

**Results**: A total of 288 patients met the inclusion criteria and were assigned into FO and no FO groups. FO occurred in 30,6% of the patients. Moderate FO occurred more frequently in comparison to severe FO (27,1% vs 6,9%). Cumulative fluid intake at day 5 was higher in the FO group (8649 ml vs. 1998 ml; p = <0,001). Also, the mean admission bodyweight was lower in the FO group (84 kg vs 75,5 kg; p = <0,001) [table 1]. In multivariate regression analysis FO was associated with a higher mean SOFA score (2,48; 95% CI [1,76-3,20]; p = <0,001) [table 2]. However, the time course (steepness) of these SOFA scores between the FO and no FO group did not differ significantly [figure 1]. Lastly, multivariate analysis revealed that FO was an independent risk factor for 28-day mortality (OR = 1,98; 95% CI [1,02-3,82]; p = 0,043) [table 2].

**Conclusions**: FO occurred in 30,6% of patients during the 5 first days of ICU admission. In most patients the FO was categorized as moderate. FO was independently associated with a higher mean SOFA score and increased 28-day mortality. The time course of these SOFA scores, however, did not differ significantly. The difference in mean admission weight between FO groups highlighted the importance of bodyweight-based fluid prescription. A prospective study to evaluate this strategy is required to translate evidences into clinical practice.

**Keywords**: *Fluid therapy, SOFA, Fluid overload, Fluid stewardship, Fluid prescription*

**References:**

1. Hawkins, W. A., Smith, S. E., Newsome, A. S., Carr, J. R., Bland, C. M., & Branan, T. N. Fluid Stewardship During Critical Illness: A Call to Action. Journal of Pharmacy Practice. 2019.
2. Malbrain ML, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, Van Regenmortel N. 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(5):361–80.
3. Woodward, C., Lambert, J., Ortiz-Soriano, V., Li, Y., Ruiz-Conejo, M., Bissell, B., Kelly, A., Adams, P., Yessayan, L., Morris, P., Neyra, J. Fluid Overload Associates With Major Adverse Kidney Events in Critically Ill Patients With Acute Kidney Injury Requiring Continuous Renal Replacement Therapy. Critical Care Medicine. 2019.
4. Malbrain, et al. Ann. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Intensive Care. 2018;8:66
5. Berthelsen, RE, Perner, A, Jensen, AK, Jensen, J-U, Bestle, MH. Fluid accumulation during acute kidney injury in the intensive care unit. Acta Anaesthesiologica Scandinavica 2018.

## Tables and Figures

**Table 1.** Characteristics of overall population according to fluid overload status.

| Characteristics | All subjects, (n=288) | No fluid overload, (n=200) | Fluid overload, (n = 88) | *p* value |
|---|---|---|---|---|
| Age, years, mean (SD) | 67,7 (15) | 66,8 (15) | 69,9 (14) | 0,108 |
| Gender, male sex, n (%) | 178 (61,8) | 124 (62,0) | 54 (61,4) | 0,918 |
| Weight at baseline, kg, mean (SD) | 81,4 (19) | 84,0 (19) | 75,5 (17) | <0,001* |
| Creatinine at baseline, median (IQR) | 87 (54) | 87 (48) | 87 (67) | 0,671 |
| APACHE IV, mean (SD) | 72,9(27,6) | 70,5(28,8) | 78,3(24) | 0,026* |
| **Reason of admission, n (%)** | | | | |
| Respiratory | 96 (33,3) | 78 (39,0) | 18 (20,5) | 0,002* |
| Sepsis | 33 (11,5) | 22 (11) | 11 (12,5) | 0,713 |
| Cardiovascular | 67 (23,3) | 51 (25,5) | 16 (18,2) | 0,176 |
| Metabolic | 4 (1,4) | 2 (1,0) | 2 (2,3) | 0,588 |
| Neurologic | 8 (2,8) | 5 (2,5) | 3 (3,4) | 0,704 |
| Trauma | 22 (7,6) | 18 (9,0) | 4 (4,5) | 0,190 |
| Post-op | 58 (20,1) | 24 (12,0) | 34 (38,6) | <0,001* |
| **Source of admission, n (%)** | | | | |
| ER | 160 (55,6) | 122 (61) | 38 (43,2) | 0,005* |
| OT | 67 (23,2) | 28 (14,0) | 39 (44,3) | <0,001* |
| Ward | 44 (15,3) | 36 (18,0) | 8 (9,1) | 0,053 |
| Others | 17 (5,9) | 14 (7,0) | 3 (3,4) | 0,234 |
| **Comorbidities, n (%)** | | | | |
| CVD | 186 (64,6) | 126 (63,0) | 60 (68,2) | 0,397 |
| DM | 56 (19,4) | 40 (20,0) | 16 (18,2) | 0,719 |
| Respiratory | 96 (33,3) | 78 (39,0) | 18 (20,5) | 0,002* |
| CKD | 30 (10,4) | 24 (12,0) | 6 (6,8) | 0,185 |
| Neurologic | 57 (19,8) | 42 (21,0) | 15 (17,0) | 0,438 |
| Malignancy | 68 (23,6) | 41 (20,5) | 27 (30,7) | 0,061 |
| Others | 63 (21,9) | 44 (22,0) | 19 (21,6) | 0,938 |
| None | 46 (16,0) | 37 (18,5) | 9 (10,2) | 0,078 |
| SOFA score at baseline, mean (SD) | 6,07 (3) | 5,45 (4) | 7,50 (3) | <0,001* |
| **Daily Fluid Balance (FB), ml, mean (SD)** | | | | |
| Day 1 | 2245 (2704) | 1086 (1313) | 4881 (3174) | <0,001* |
| Day 2 | 1372 (1993) | 771 (1258) | 2739 (2601) | <0,001* |
| Day 3 | 382 (1550) | 172 (1161) | 858 (2122) | 0,005* |
| Day 4 | 88 (1475) | 20 (1915) | 228 (1915) | 0,443 |
| Day 5 | -52 (1229) | -91 (1160) | 32 (1379) | 0,587 |
| Daily average FB during ICU stay, ml, mean (SD) | 1001 (1270) | 491 (708) | 2160 (1489) | <0,001* |
| Cumulative FB from day 1 to day 5, ml, mean (SD) | 4030 (4928) | 1998 (2976) | 8649 (5396) | <0,001* |
| **Clinical parameters** | | | | |
| Average SOFA score during ICU stay, mean (SD) | 5,23 (3) | 4,49 (3) | 6,55 (3) | <0,001* |
| ICU LOS, median (IQR) | 4 (4) | 4 (4) | 4 (4) | 0,361 |
| 28-day mortality, n (%) | 58 (20,1) | 35 (17,5) | 23 (26,1) | 0,092 |

*statistically significant

**Table 2.** Outcomes after regression analysis (logistic and linear)

| Variables | Crude analysis | 95% CI | *p* value | Adjusted analysis | 95% CI | *p* value |
|---|---|---|---|---|---|---|
| Mean SOFA, *mean difference* | 2,06 | [1,35-2,77] | <0,001# | 2,48* | [1,76-3,20] | <0,001# |
| 28-day mortality, *OR* | 1,668 | [0,92-3,04] | 0,094 | 1,98** | [1,02-3,82] | 0,043# |

*Adjusted for confounders (reason of admission)
**Adjusted for confounders (reason of admission, weight, age)
# Statistically significant

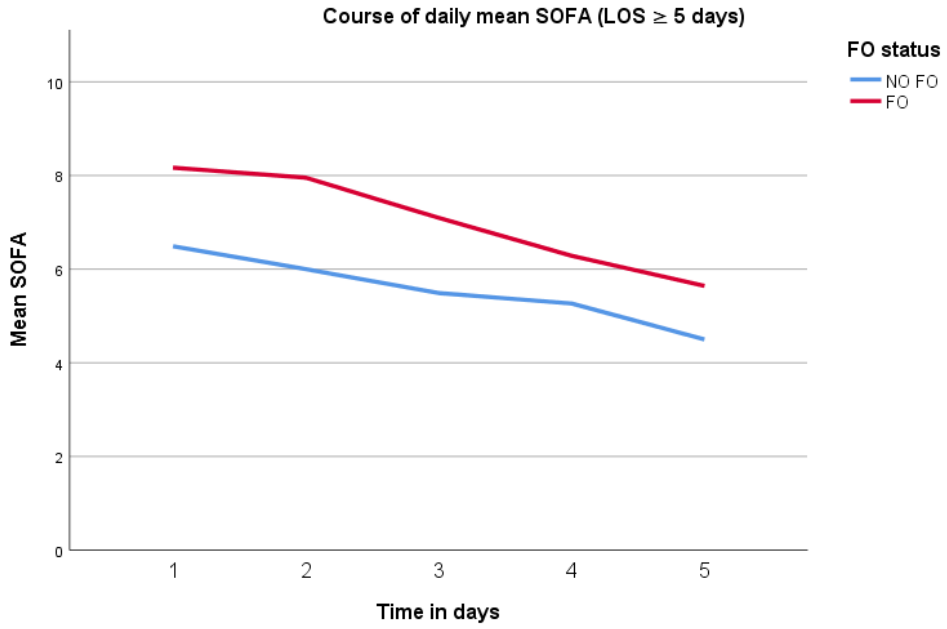


**Figure 1.** Course of daily mean SOFA in time for patients with Length of stay (LOS) ≥ 5 days. Steepness of the lines were not significantly different (p= 0.314).