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ORIGINAL

Long-term effects of restriction of intravenous fluid in adult ICU patients with septic shock

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Abstract

Purpose: To assess long-term outcomes of restrictive versus standard intravenous (IV) fluid therapy in adult intensive care unit (ICU) patients with septic shock included in the European Conservative versus Liberal Approach to Fluid Therapy in Septic Shock in Intensive Care (CLASSIC) trial.

Methods: We conducted the pre-planned analyses of mortality, health-related quality of life (HRQoL) using EuroQol (EQ)-5D-5L index values and EQ visual analogue scale (VAS), and cognitive function using Mini Montreal Cognitive Assessment (Mini MoCA) test at 1 year. Deceased patients were assigned numerical zero for HRQoL as a state equal to death and zero for cognitive function outcomes as worst possible score, and we used multiple imputation for missing data on HRQoL and cognitive function.

Results: Among 1554 randomized patients, we obtained 1-year data on mortality in 97.9% of patients, HRQoL in 91.3%, and cognitive function in 86.3%. One-year mortality was 385/746 (51.3%) in the restrictive-fluid group versus 383/767 (49.9%) in the standard-fluid group, absolute risk difference 1.5%-points [99% confidence interval (CI) − 4.8 to

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7.8]. Mean differences were 0.00 (99% CI − 0.06 to 0.05) for EQ-5D-5L index values, − 0.65 for EQ VAS (− 5.40 to 4.08), and − 0.14 for Mini MoCA (− 1.59 to 1.14) for the restrictive-fluid group versus the standard-fluid group. The results for survivors only were similar in both groups.

Conclusions: Among adult ICU patients with septic shock, restrictive versus standard IV fluid therapy resulted in similar survival, HRQoL, and cognitive function at 1 year, but clinically important differences could not be ruled out.

Keywords: Septic shock, Sepsis, Intravenous fluid, Critical illness, Long-term outcomes, Quality of life, Cognitive function

Background

Septic shock results in millions of deaths every year [1, 2], and the survivors often have long-term sequelae with physical, psychological, cognitive, and social implications [3–5].

Intravenous (IV) fluid is a first-line treatment, as suggested in the Surviving Sepsis Campaign guideline [1]. While short-term outcomes of lower vs. higher fluid volumes may be similar in patients with septic shock [6–8], no randomized trial of different IV fluid volumes has reported on long-term health-related quality of life (HRQoL) or any outcomes beyond 90 days for patients with septic shock [9].

In patients with acute lung injury, 1-year follow-up of the Fluid and Catheter Treatment Trial (FACTT) allocation to the conservative vs. liberal fluid management was potentially associated with long-term cognitive impairment and reduced executive function, but a similar quality of life was found [10]. However, only 75 of 439 survivors were eligible for 1-year follow-up assessments [11].

The Conservative vs. Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care (CLASSIC) trial assessed IV fluid restriction vs. standard IV fluid therapy and found similar mortality and other outcomes in the two intervention groups at 90 days [6]. In this report, we present the results of the pre-planned assessment of mortality, HRQoL, and cognitive function at 1 year in the CLASSIC trial [12]. We hypothesized that fluid restriction would improve long-term outcomes.

Take-home message

In adult ICU patients with septic shock, restrictive vs. standard intravenous fluid therapy resulted in similar survival, health-related quality of life, and cognitive function at 1 year.

Methods

Trial design

The CLASSIC trial was a European, investigator-initiated, stratified, parallel-group, open-labeled randomized trial. The trial protocol was approved by the relevant medicine agencies and ethics committees [6]. The trial protocol, statistical analysis plan, and primary results have been published elsewhere [6, 13]; so has the statistical analysis plan for the 1-year outcomes [12]. Some deviations from the protocol and analysis plan were necessary; these are outlined with rationales in the Electronic Supplementary Material (ESM1). We report this manuscript according to the CONSORT 2010 Statement (checklist in ESM2).

Trial sites and patients

Patients were enrolled from November 2018 to November 2021, in 31 intensive care units (ICUs) in Denmark, Sweden, Norway, Switzerland, Italy, the Czech Republic, the United Kingdom, and Belgium after written informed consent from patients or their legal surrogates according to national regulations [13].

We enrolled adult ICU patients with septic shock according to the SEPSIS-3 criteria [14], who had received at least 1L of IV fluid in the last 24 h, and onset of shock no longer than 12 h before screening. Further details regarding the inclusion and exclusion criteria are presented in the ESM1 and elsewhere [6, 13].

Outcomes

The pre-specified secondary outcomes assessed 1 year after randomization were all-cause mortality, HRQoL, and cognitive function [12]. To increase follow-up rate and uniform data collection, we made a standard operating procedure (in the ESM1) for all patients [15]. Trial staff made several attempts to obtain follow-up data for at least 4 weeks after the 1-year date. The process was centrally monitored by the coordinating center in Denmark to support sites in obtaining responses. Data were obtained from medical records (i.e., survival status) and by phone interviews with survivors in their native language. Survivors were interviewed over the telephone by certified trial staff (ESM1) who were masked for the intervention using EuroQol 5 dimension 5 levels (EQ-5D-5L) questionnaire and EQ visual analogue scale (EQ

VAS) [16, 17] and Mini Montreal Cognitive Assessment (MoCA) test [18]. In some cases, relatives provided data on survival status or, if necessary, performed the HRQoL on behalf of the patient (using the proxy version of the tool). Relatives could not perform the cognitive test.

The EQ-5D-5L is a generic instrument to describe and value health and has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response levels: no, slight, moderate, severe, or extreme problems [16, 17]. It also includes EQ VAS, for which respondents are asked to mark on a visual analogue scale how good or bad their health is on the day of the questionnaire on a scale from 100 ('the best health you can imagine') to 0 ('the worst health you can imagine'). When EQ VAS was performed by phone, respondents were asked to picture a scale like a thermometer as per recommendations in the EuroQol interview guide.

The HRQoL outcome measures were EQ-5D-5L index values, a summary score based on the 5 domains reflecting health states according to the preference of a general population ranging from 1.0 (perfect health) to values below 0 (health states valued worse than death, with 0 defined as a state equal to death) and EQ VAS [17]. We used country-specific value sets to calculate the index values for Denmark [19], Sweden [20], England [21], and Italy [22]. The lowest index value depends on the value set, and for Denmark, the lowest index value is − 0.76 [19]. For countries with no specific value set, we contacted the national investigator and agreed on a value set close to that country as for culture and healthcare system. For Switzerland, we used the German value set [23]; for Norway, the Danish value set [19]; and for Czech Republic, the Polish value set [24]. As recommended, we conducted an additional analysis with index values calculated using the Danish value set [19] for all patients (most patients were enrolled in Denmark) [25].

The Mini MoCA is a short version of the MoCA test [18] validated for telephone use [26]. The Mini MoCA consists of 4 cognitive dimensions: attention (immediate recall of 5 words), executive functions and language (1-min verbal fluency), orientation (6 items on date and geographic orientation), and memory (delayed recall and recognition of 5 previously learned words). The total score ranges from 0 to 30, with lower values indicating worse cognitive function. To correct for any educational effect on the cognitive test, 1 point is added for participants with 12 years of education or less (scores were truncated at the maximum upper value of 30 points) [27]. Further details on the Mini MoCA are presented in the ESM1.

Statistical analyses

We deviated from the predefined analysis plan in the following ways [12]: (1) HRQoL and Mini MoCA were non-normally distributed, hence why we used Kryger Jensen and Lange test only [28], (2) statistical handling of mortality was not clearly specified; we primarily used adjusted logistic regression models with G-computation and non-parametric bootstrapping, (3) we added secondary analyses in survivors only, (4) we added best–worst and worst–best case scenario sensitivity analyses for missing data despite Little's test rejected data being missing completely at random (described in detail, with reasoning, in ESM1).

The analysis population consisted of all randomized patients ($n = 1554$) except 5, who withdrew consent for the use of all data. We present descriptive baseline data stratified by treatment allocation and survival/respondence status for HRQoL and cognitive outcomes. Numerical data were summarized using medians with interquartile ranges (IQRs) and categorical data were summarized using numbers with percentages.

As more than 5% of the patients had missing outcome data (8.8% for EQ-5D-5L index values, 9.2% for EQ VAS, and 13.8% for Mini MoCA), we conducted Little's test, which indicated that data were not missing completely at random ($P < 0.001$). Consequently, we conducted the primary analyses of these outcomes after multiple imputation of missing data [29]. We used the predictive mean matching method with 50 datasets imputed separately in each treatment group, with the imputation model including the stratification variables (trial site and metastatic or hematologic cancer), baseline values, and all outcomes (ESM1). Analysis was conducted in each imputed dataset with results pooled as appropriate [30]. Additionally, we conducted best–worst and worst–best case imputations of missing data using the mean ± 1 standard deviation (SD) of EQ-5D-5L index, EQ VAS, and Mini MoCA using the means and SDs estimated in survivors with complete responses for survivors with missing data, and in all patients with available data for patients with missing survival status, and complete case analyses, which we also used for the mortality outcome due to limited missing data (2.1%).

The primary analysis of all outcomes was adjusted for stratification variables, whereas secondary analysis was unadjusted. We analyzed mortality at 1 year using a G-computation procedure based on an adjusted logistic regression model, and 50,000 bootstrap resamples (for the primary analysis), and generalized linear models with binomial error distributions and log/identity links for the unadjusted, secondary analysis. Results are presented as average (unconditional) risk differences (RDs) and relative risks (RRs) with 99% confidence intervals

(CIs), supplemented with a Kaplan–Meier survival curve. The continuous outcomes were clearly non-normally distributed, as expected. For the continuous outcomes, we used the Kryger Jensen and Lange test [28] to calculate *P* values and linear regression models with a similar procedure as for the primary analysis of mortality and presented average (unconditional) mean differences (MDs) and ratios of means with 99% CIs. For the primary analyses of the numerical outcomes, patients who had died at 1 year were included in the analyses with scores of zero. This corresponds to a health state equivalent to death for EQ-5D-5L index values or the worst possible perceived health state value for EQ VAS or the worst cognitive function score [17]. We also analyzed EQ-5D-5L index values, EQ VAS, and Mini MoCA in survivors only. Finally, we analyzed EQ-5D-5L index values for all patients using the Danish value set in secondary analyses of all patients and survivors only, respectively.

Analyses were performed using R (R Core Team, Foundation for Statical Computing, Vienna, Austria), versions 4.2.0 and 4.2.1. *P* values below 0.01 were considered statistically significant due to multiple testing [12].

Results

A total of 1549 patients were included in 1-year follow-up analysis (Fig. 1). There were no major differences in baseline characteristics between the allocation groups (Table 1). Some differences were present between vital/response status strata: 1-year nonsurvivors had more coexisting conditions, were more frequently admitted from in-hospital wards, had higher median predicted 90-day mortality [31], more frequently had sepsis due to gastrointestinal infection, and more frequently received life-supportive interventions than survivors (respondents and nonrespondents). Nonrespondents appeared less ill (more had admissions from emergency department/prehospital or operation/recovery room and more had urinary tract infection) than respondents.

1-Year mortality

We obtained 1-year mortality data for 97.9% of the 1554 randomized patients. One year after randomization, 385 of 767 (51.3%) in the restrictive-fluid group had died compared with 383 of 782 (49.9%) in the standard-fluid group, leading to an absolute difference of 1.5%-points (99% CI − 4.8 to 7.8; $P=0.55$) (Table 2 and Table S1). The Kaplan–Meier survival curve is presented in Fig. 2A.

Health-related quality of life

We obtained 1-year HRQoL for 91.3% of the 1554 randomized patients. The time from the 1-year follow-up date to complete HRQoL assessment was a median 6 days (IQR 3–14) in the restrictive-fluid group and median 5 days (IQR 3–17) in the standard-fluid group. The proportions of relatives answering the HRQoL questionnaire were 24 of 365 (6.6%) in the restrictive-fluid group and 21 of 384 (5.5%) in the standard-fluid group.

Patients in the restrictive-fluid group had a median EQ-5D-5L index value of 0 (IQR 0–0.82) compared with 0 (IQR 0–0.81) in the standard-fluid group, leading to an MD of 0 (99% CI − 0.06–0.05; $P=0.81$, Table 2 and Fig. 2B). The median EQ VAS was 0 (IQR 0–70) in both groups with an MD of − 0.65 (99% CI − 5.4 to 4.08; $P=0.8$, Table 2 and Fig. 2B). Results for survivors only are presented in Table 2 and Table S1 in the ESM1. EQ-5D-5L index values were 0.83 (IQR 0.58–0.93) vs. 0.81 (IQR 0.58–0.93) for the restrictive- vs. the standard-fluid groups, respectively, with an MD of 0.01 (99% CI − 0.05 to 0.07; $P=0.61$). One-year data for the survivors for each EQ-5D-5L domain are presented in Fig. 3 and Table S2 in the ESM1.

Cognitive function

We obtained 1-year cognitive function for 86.3% of the 1554 randomized patients. The median time from the 1-year follow-up date to complete cognitive function assessment was 6 days (IQR 3–14.5) in the restrictive-fluid group and 6 days (IQR 3–17) in the standard-fluid group. The length of education was median 11 years (IQR 9–14) for both groups.

The median Mini MoCA scores were 0 (IQR 0–22) in both groups leading to an MD of -0.14 (99% CI − 1.59 to 1.31; $P=0.82$) (Table 2). Similar MDs were found in the analyses of survivors only (Table S1 in the ESM1). The four domains of cognitive function for survivors only are presented in Table S3 in ESM1.

Sensitivity analyses

The results from the complete case analyses and unadjusted analyses were similar to the primary results except the best–worst, worst–best case scenarios due to moderate proportions of missing data (Table S1, ESM1).

Discussion

In this 1-year follow-up study of the CLASSIC trial, we found that adult ICU patients with septic shock randomized to restrictive-fluid therapy vs. standard-fluid therapy had similar survival, HRQoL, and cognitive function at 1 year. However, we cannot exclude a clinical important difference in mortality as the 99% CI ranged from − 4.8 to 7.8.

Our results are in line with those from the previously mentioned systematic review with meta-analysis in patients with sepsis or septic shock, where the RR for

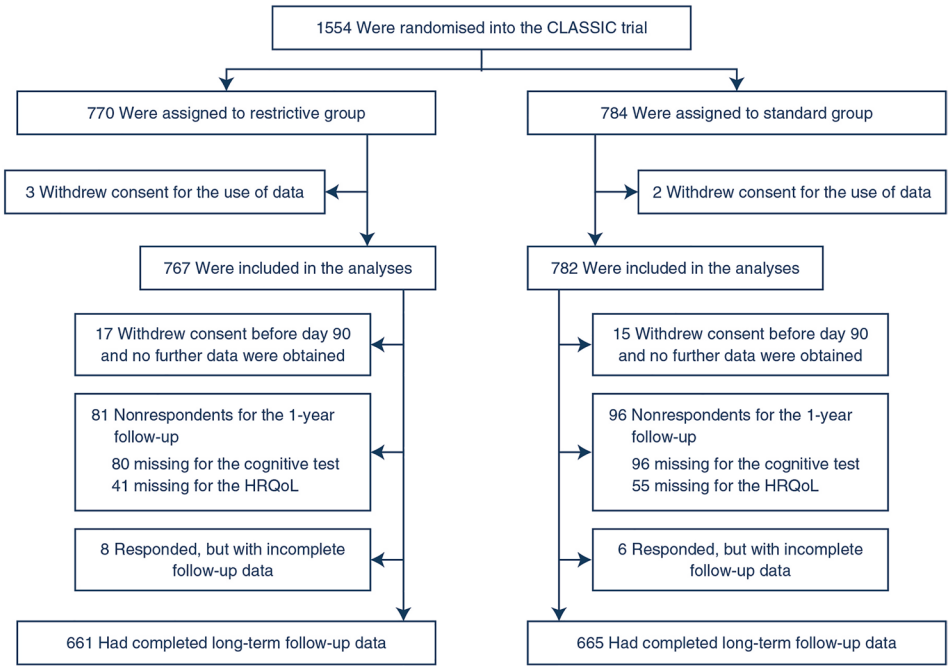

Fig. 1 CONSORT diagram of the patient flow in the CLASSIC trial. Details up to day 90 were presented in the primary report [6]. We included all patients randomised ($n = 1554$) except for 5 patients excluded before day 90 ($n = 1549$). There were patients who withdrew consent up to day 90 follow-up ($n = 32$) where the primary outcome was published [6] for whom no further data were obtained. For nonrespondents we registered reasons for being lost to follow at 1 year with a detailed description of missing data available in Tables S4 and S5 in the ESM1. Patients who responded, but had incomplete data was due to partly fulfilled HRQoL questionnaire or partly performed cognitive test

all-cause mortality was 0.99 (97% CI 0.89–1.1) closest to day 90 after randomization being the longest follow-up in eight low risk of bias trials [9].

We are not aware of any studies assessing HRQoL on patients with septic shock defined by the Sepsis-3 criteria [14]. The early goal-directed therapy trial, Australasian Resuscitation In Sepsis Evaluation (ARISE), included patients with early septic shock in the emergency department [32] using the sepsis criteria from 1992 [33]. The 90-day mortality was 18.6% in the early goal-directed therapy (EGDT) group and 18.8% in the usual-care group, which can likely be explained by a younger population and fewer patients receiving vasopressor and mechanical ventilation [32]. The 1-year HRQoL assessed with EQ-5D-3L in survivors only was lower than in our cohort, which could be due to the three-level instrument with a ceiling effect [33, 34] or our population with low scores being the nonsurvivors; however, EQ VAS results were similar to ours. The ongoing ARISE FLUIDS trial (ClinicalTrials.gov identifier: NCT04569942) compares restricted fluids and early vasopressors to larger initial IV fluid volumes with later vasopressor administration in patients with sepsis, hypotension, and elevated lactate in emergency departments and will provide further data on HRQoL after 1 year using EQ-5D-5L.

The only fluid trial we are aware of assessing cognitive function is the previously mentioned FACTT trial where patients with acute lung injury who received conservative vs. liberal fluid management had worse cognitive impairment after 2 months and 1 year, respectively [11]. We did not find similar results which can possibly be explained by the small population that was much younger and only 20–25% had sepsis [11]. Anyway, cognitive function is an important outcome, especially as sepsis is associated with deterioration of the cognitive performance [35]. Overall, our patients scored a median 22 points out of 30 on the Mini MoCA test. For the original MoCA test, the cut-off for mild cognitive impairment is < 26. Our results do appear to confirm findings in observational studies of cognitive deterioration in survivors of septic shock [5, 35].

Strengths and limitations

Our study has several strengths. First, we had almost complete data for mortality and only moderate missingness for HRQoL. Second, cognitive function was assessed by certified staff to increase interrater reliability by adhering to a uniform standard operating procedure. Third,

Table 1 Baseline characteristics in all 1549 patients analyzed in the CLASSIC trial stratified by allocation and status at follow-up

	Dead at 1-year follow-up		Alive with complete long-term follow-up		Any missing outcome data	
	Restrictive-fluid group ($n=385$)	Standard-fluid group ($n=383$)	Restrictive-fluid group ($n=276$)	Standard-fluid group ($n=282$)	Restrictive-fluid group ($n=106$)	Standard-fluid group ($n=117$)
Age	73 (66–79)	71 (64–78.5)	67 (59–75)	65.5 (56–74)	67 (55–76)	70 (59–76)
Male sex	236 (61.5%)	223 (58.2%)	169 (61.2%)	167 (59.2%)	54 (52.4%)	64 (56.6%)
Coexisting conditions						
Hematologic or metastatic cancer	97 (25.2%)	96 (25.1%)	24 (8.7%)	35 (12.4%)	8 (7.5%)	9 (7.7%)
Ischemic heart disease or heart failure	65 (16.9%)	80 (20.9%)	41 (14.9%)	51 (18.1%)	11 (10.7%)	21 (18.6%)
Chronic hypertension	189 (49.2%)	183 (47.8%)	125 (45.3%)	135 (47.9%)	33 (32%)	42 (37.2%)
Long-term dialysis	8 (2.1%)	9 (2.3%)	1 (0.4%)	2 (0.7%)	0 (0%)	1 (0.9%)
Time from ICU admission to randomization	3.4 (1.6–7.9)	3.8 (1.7–8.6)	3.0 (1.2–6.8)	2.9 (1.3–7.9)	2.8 (1.4–6.9)	2.9 (1.4–6.7)
Predicted 90-day mortality (SMS-ICU [31])	24 (21–27)	24 (20–27)	22 (18.8–24)	20 (17–23)	22 (19–24)	21 (17–24)
Admission from						
Emergency department or prehospital	144 (37.5%)	142 (37.1%)	110 (39.9%)	113 (40.1%)	45 (43.7%)	45 (39.8%)
Hospital ward	154 (40.1%)	161 (42%)	77 (27.9%)	103 (36.5%)	32 (31.1%)	36 (31.9%)
Operating or recovery room	76 (19.8%)	68 (17.8%)	75 (27.2%)	60 (21.3%)	23 (22.3%)	26 (23%)
Another ICU	10 (2.6%)	12 (3.1%)	14 (5.1%)	6 (2.1%)	3 (2.9%)	6 (5.3%)
Focus of infection						
Gastrointestinal	150 (39.1%)	160 (41.8%)	103 (37.3%)	99 (35.1%)	29 (28.2%)	39 (34.5%)
Pulmonary	121 (31.5%)	117 (30.5%)	63 (22.8%)	57 (20.2%)	26 (25.2%)	32 (28.3%)
Urinary tract	33 (8.6%)	40 (10.4%)	57 (20.7%)	71 (25.2%)	31 (30.1%)	23 (20.4%)
Skin or soft tissue	33 (8.6%)	26 (6.8%)	22 (8%)	30 (10.6%)	8 (7.8%)	8 (7.1%)
Other	47 (12.2%)	40 (10.4%)	31 (11.2%)	25 (8.9%)	9 (8.7%)	11 (9.7%)
Body weight, blood values, and interventions						
Body weight (kg)	76 (67–86)	76 (65–90)	82.5 (70–96)	81 (70–96.8)	73 (61.5–85)	76 (65–88)
Highest plasma lactate (mmol/liter)	4 (2.8–7.1)	4.3 (2.8–7.3)	3.5 (2.6–5.1)	3.5 (2.6–5.4)	3.5 (2.7–5.8)	3.6 (2.8–4.9)
Highest dose of norepinephrine (µg/kg/min)	0.3 (0.1–0.5)	0.3 (0.1–0.5)	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.2 (0.1–0.4)	0.2 (0.1–0.4)
Volume of intravenous fluid 24 h before randomization (ml)	3000 (1995–4367)	3000 (1969–5000)	3273.5 (2000–5000)	3000 (2000–4782.5)	3725 (2711–5186.5)	3150 (2225–4400)
Systemic glucocorticoid	119 (31%)	121 (31.6%)	79 (28.6%)	81 (28.7%)	21 (20.4%)	25 (22.1%)
Highest plasma creatinine (µmol/liter)	150 (97–247)	156 (101.5–231.8)	132 (93–208)	140 (95–219)	126 (79–193)	134 (89.8–224)
Respiratory support	213 (55.5%)	213 (55.6%)	137 (49.6%)	115 (40.8%)	52 (50.5%)	51 (45.1%)

SMS: simplified mortality score

Numeric data are presented as medians with interquartile ranges, and categorical data as number and percentages

The analysis population consisted of all randomized patients except 5, who withdrew consent for the use of all data ($n=1549$). Baseline characteristics are stratified by

Table 1 (continued)

allocation, vital status, and response status at 1 year. There were 8 patients with missing data (0.5%) for all variables except for the highest plasma creatinine with 17 patients with missing data (1.1%). There are 10 more patients with available baseline data compared to the CLASSIC primary publication [6] as we obtained consent to use the baseline data in anonymised form without further follow-up

Table 2 Outcomes at 1-year follow-up

Variable	Restrictive-fluid group ($n=767$)	Standard-fluid group ($n=782$)	Adjusted risk difference or adjusted mean difference (99% CI)	Adjusted relative risk or adjusted ratio of means (99% CI)	*P* value[a]	Missing values
Mortality						
Death by 1 year	385 (51.3%)	383 (49.9%)	1.5% (− 4.8% to 7.8%)	1.03 (0.91–1.17)	0.55	32 (2.1%)
Health-related quality of life						
EQ-5D-5L index values[b]	0 (0–0.82)	0 (0–0.81)	0 (− 0.06 to 0.05)	0.99 (0.85–1.16)	0.81	135 (8.7%)
Survivors only[c]	0.83 (0.58–0.93)	0.81 (0.58–0.93)	0.01 (− 0.05 to 0.07)	1.01 (0.93–1.1)	0.61	102 (13.6%)
EQ VAS	0 (0–70)	0 (0–70)	− 0.65 (− 5.4 to 4.08)	0.98 (0.84–1.14)	0.80	140 (9%)
Survivors only[c]	70 (50–80)	70 (50–80)	− 0.05 (− 5.29 to 5.25)	1 (0.92–1.09)	0.63	108 (14.4%)
Cognitive test[d]						
Mini MoCA	0 (0–22)	0 (0–22)	− 0.14 (− 1.59 to 1.31)	0.99 (0.86–1.14)	0.82	212 (13.7%)
Survivors only[c]	22 (17.5–25)	22 (18–24.5)	0.16 (− 0.96 to 1.39)	1.01 (0.95–1.07)	0.59	180 (24%)

CI confidence interval, *EQ-5D-5L:* EuroQol 5 domains 5 levels, *VAS* visual analogue scale, *MoCA* Montreal cognitive assessment

Numeric data are presented as medians with interquartile ranges, and categorical data as numbers and percentages

The analysis population consisted of all randomized patients except 5, who withdrew consent for the use of all data ($n=1549$). Patients with missing values include patients lost to follow-up and patients who withdraw consent ($n=43$)

[a] All analyses were adjusted for the stratification variables, which were trial site and hematologic or metastatic cancer at baseline. Results are presented as adjusted, unconditional, average treatment effects

[b] Index values calculated using country-specific value sets, as described in the Methods section

[c] Post hoc analyses

[d] Nonsurvivors at 1 year after randomization were assigned the value zero corresponding to a health state as bad as being dead for EQ-5D-5L index values and the worst possible score for EQ VAS and Mini MoCA. Missing data were multiply imputed and all HRQoL and cognitive function results in this table (including descriptive data) were calculated using the multiply imputed datasets. We collected data for EQ-5D-5L index values for 1,414 (91.3%) patients, for EQ VAS scores for 1,409 (91%) patients, and for Mini MoCA for 1,337 (86.3%) patients

outcome assessors interviewing patients were masked to the allocation. Finally, CLASSIC was a large European trial involving 31 ICUs in 8 countries, which increases external validity.

Our study also has limitations. First, the proportion of missing data for HRQoL and cognitive function was more than 5%. However, we handled this using multiple imputations, supplemented with best–worst and worst–best case scenarios, which showed that missing data potentially could affect the results in both directions [12, 36]. Second, the trial allocation was not masked for patients and relatives, which may have affected the assessment of HRQoL and cognitive function. Third, the Mini MoCA is a cognitive test developed to detect mild cognitive impairment [18] and has not been validated in critically ill patients, and we cannot assure the mentioned cut-off is reasonable for our population due to the use of the shortened version of the tool by telephone. However the full MoCA has been preliminary validated for patients with septic shock [37]. Further, we may have underestimated the cognitive function as patients surviving sepsis have been described to have moderate-to-severe impairment of cognitive function [5], but Mini MoCA detects only mild cognitive function. We found that the Mini MoCA was feasible to use by telephone but posed some challenges in patients with impaired hearing and those too ill to comply. Fourth, as relatives were not able to assess the cognitive function as proxy for the patient, we had a higher proportion of missing data for this outcome. Fifth, the assignment of the value zero to deceased patients may be discussed. We expected that the population would have high mortality and planned this assignment in both HRQoL and cognitive function. We hypothesized that the intervention may affect mortality which is the reason, hence why a survivors-only analysis would have been misleading, as discussed in a recent scoping review [38] and by Colantuoni and colleagues [39]. EuroQol recommends to use zero as index value for deceased patients, because this has been valued as a health state equal to death [17]. Also including survivors

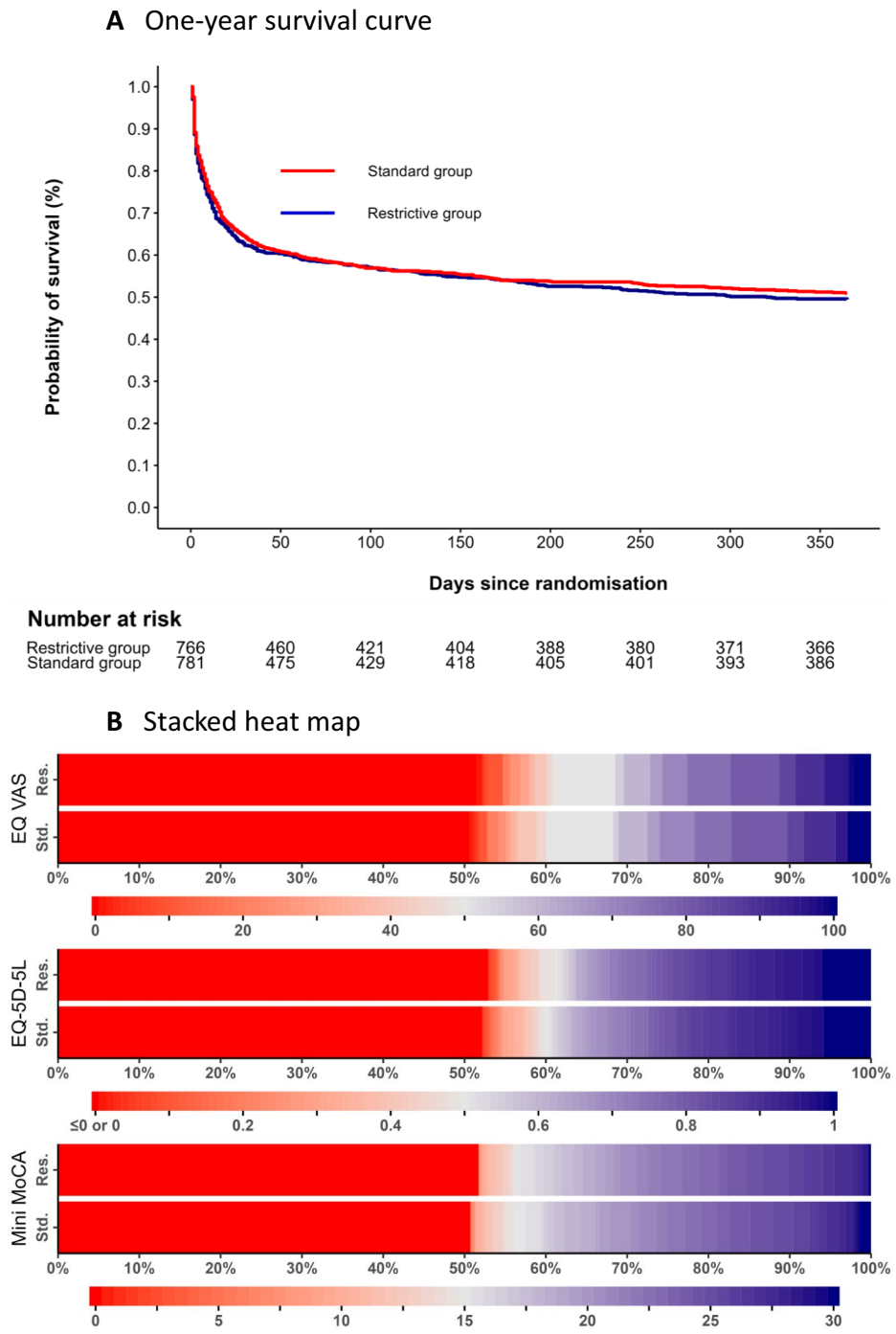

Fig. 2 One-year survival curves in the two interventions groups (**A**). One patient in each group had died at day 90, but dates of death were unknown due to lack of consent. This resulted in 766 patients in the restrictive group and 781 patients in the standard group to be presented in the survival curves. The four patients who were lost to follow-up at day 90 [4] were included in the survival curves until the last day they were known to be alive. **B** Stacked heat maps for EQ VAS, EQ-5D-5L index, and Mini MoCA values in all patients after imputations (nonsurvivors assigned zero and multiple imputation of missing data) in the restrictive (Res.) vs standard (Std.) groups. Red represents worse outcomes and blue better outcomes. The horizontal axes represent the cumulated proportion of the patients scoring at or below the value on the secondary axes which represents the score ranges of the tools used; EQ VAS from 0 to 100, EQ-5D-5L index value from below 0 (corresponding to health states valued worse than death) to 1 and Mini MoCA from 0 to 30. In total, 1.5% (restricted-fluid group) and 1.6% (standard-fluid group) of the EQ-5D-5L index values were below zero; these were included as zero in heat map. The plots were done by calculating the proportions after stacking all 50 imputed datasets. Heat maps for survivors only are presented in the ESM1

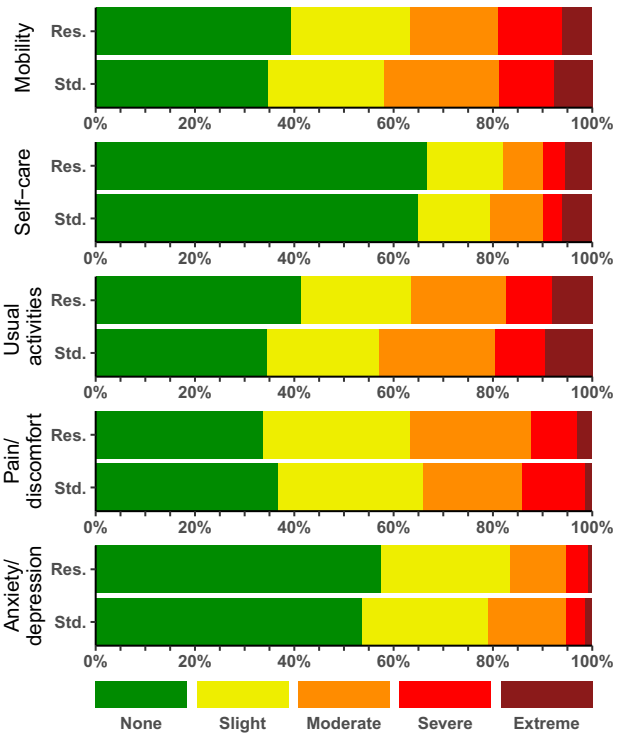

Fig. 3 Distribution of the health state levels in the 5 HRQoL domains from all respondents being alive at 1-year ($n = 749$) in the restrictive (Res.) vs. standard (Std.) groups. Relatives responded on behalf of 55/749 (7.3%) of the surviving patients. The numeric data corresponding to the Figure are presented in Table S3 in the ESM1

only would have excluded the contribution of half of our population, which would lead to loss of important information and decrease power [28, 39]. Thus, we found it most appropriate to include the deceased cohort in our primary analyses. Sixth, more patients had gastrointestinal focus of infection than respiratory focus [6]. Finally, different results may be obtained in settings where higher IV fluid volumes are given as standard care [6, 40].

Conclusions

In conclusion, restrictive IV fluid therapy resulted in similar survival, HRQoL, and cognitive function at 1 year in adult ICU patients with septic shock compared with standard-fluid therapy, but clinically important differences could not be excluded.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-023-07114-8.

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Author contributions
MBNK coordinated the follow-up and wrote the first draft, which was critically revised by all authors. TSM and PS were coordinating investigators of the CLASSIC trial. AG conducted all analyses presented in this manuscript. Author contributions to the design and conduct of the CLASSIC trial together with complete trial were presented in the CLASSIC primary publication [6].

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Data availability
De-identified trial patient data set will be shared. Data will be available to researchers who provide a methodologically sound proposal.

Declarations

Conflicts of interest
MBNK, TSM, PS, AG, PBH, MBM, MHM, GVK, and AP are affiliated with the Department of Intensive Care at Rigshospitalet, which has received funding for other projects from The Novo Nordisk Foundation, Pfizer, and Fresenius Kabi, Sygeforsikringen "danmark", and has conducted contract research for AM-Pharma (the REVIVAL trial). AP has received an honorarium from Novartis for the participation in an advisory board. MHB and SW are affiliated with the Department of Anaesthesia and Intensive Care at Copenhagen University Hospital – North Zealand, which has received funding for other research projects from The Novo Nordisk Foundation, Sygeforsikringen "danmark", Toyota Foundation, A.P. Moeller Foundation, Frimodt-Heineke Foundation, Svend Andersen Foundation, Ehrenreich Foundation, and Olga Bryde Nielsen Foundation, and has conducted contract research for AM-Pharma (the REVIVAL trial) and Inotrem (ASTONISH trial). MHB has received an honorarium from AM-Pharma for participation in an advisory board. All other authors have no conflicts to disclose.

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