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ORIGINAL

# Small volume resuscitation with 20% albumin in intensive care: physiological effects

## The SWIPE randomised clinical trial

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**Abstract**

**Purpose:** We set out to assess the resuscitation fluid requirements and physiological and clinical responses of intensive care unit (ICU) patients resuscitated with 20% albumin versus 4–5% albumin.

**Methods:** We performed a randomised controlled trial in 321 adult patients requiring fluid resuscitation within 48 h of admission to three ICUs in Australia and the UK.

**Results:** The cumulative volume of resuscitation fluid at 48 h (primary outcome) was lower in the 20% albumin group than in the 4–5% albumin group [median difference −600 ml, 95% confidence interval (CI) −800 to −400; $P<0.001$]. The 20% albumin group had lower cumulative fluid balance at 48 h (mean difference −576 ml, 95% CI −1033 to −119; $P=0.01$). Peak albumin levels were higher but sodium and chloride levels lower in the 20% albumin group. Median (interquartile range) duration of mechanical ventilation was 12.0 h (7.6, 33.1) in the 20% albumin group and 15.3 h (7.7, 58.1) in the 4–5% albumin group ($P=0.13$); the proportion of patients commenced on renal replacement therapy after randomization was 3.3% and 4.2% ($P=0.67$), respectively, and the proportion discharged alive from ICU was 97.4% and 91.1% ($P=0.02$).

**Conclusions:** Resuscitation with 20% albumin decreased resuscitation fluid requirements, minimized positive early fluid balance and was not associated with any evidence of harm compared with 4–5% albumin. These findings support the safety of further exploration of resuscitation with 20% albumin in larger randomised trials.

**Trial registration:** http://www.anzctr.org.au. Identifier ACTRN12615000349549.

**Keywords:** Albumin, Fluid therapy, Critical care, Resuscitation

## Introduction

Intravenous fluid resuscitation is a common treatment for haemodynamic instability in intensive care unit (ICU) patients. However, the beneficial effect of early plasma volume expansion may be counteracted by increased capillary permeability, fluid extravasation and fluid accumulation in tissues [1]. Compared with crystalloid solutions, resuscitation with human albumin solutions preserves plasma colloid oncotic pressure, induces greater intravascular volume expansion, attenuates fluid accumulation and, in post hoc analyses, appears to improve survival in subgroups of patients with sepsis or septic shock [2, 3].

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Human albumin solutions are either similar to plasma concentration (4% in Australia and New Zealand and 5% in the UK) or more concentrated (20–25%). Experimental human data indicate that the volume-expanding effect of 4–5% albumin is approximately equal to the infused volume, whereas the volume-expanding effect of 20% albumin approximates twice the infused volume [4–9]. In addition, observational clinical data suggest that a greater volume might be required for resuscitation with 4% albumin than with 20% albumin to achieve the same haemodynamic response [10]. Such small volume resuscitation should logically lead to less fluid accumulation and attenuate the widely documented adverse consequences of positive fluid balances [11–15]. However, whether 20% albumin has a similar volume-expanding effect in states of significant capillary leakiness (e.g. in septic shock) remains uncertain.

Despite the above theoretical advantage of "small volume resuscitation" with 20% albumin, there is concern that rapid administration of 20% albumin may induce a hyperoncotic state, which may cause decreased glomerular filtration rate (GFR) and lead to insufficient intravascular volume expansion [16–18]. However, whether these effects occur in the clinical context is unclear. Moreover, the effects of 20% albumin resuscitation on volume requirements, fluid balance, physiological and biochemical responses have not been systematically investigated in a randomised controlled trial.

Accordingly, we designed and completed the Small volume resuscitation With albumin in Intensive care: Physiological Effects (SWIPE) randomised trial to compare resuscitation volume requirements, fluid balance, and biochemical and physiological efficacy of 20% albumin vs. 4–5% albumin for fluid resuscitation in ICU patients. We aimed to test the hypothesis that, compared with 4–5% albumin, resuscitation with 20% albumin would decrease the volume of resuscitation fluid administered and lead to a less positive fluid balance in the first 48 h after randomisation.

## Methods

### Study design

We conducted an investigator-initiated, parallel-group, open-label randomised controlled trial including adult surgical and medical patients admitted to three ICUs of three hospitals in Australia and the UK. Since 20% albumin is provided in 100-ml bottles and 4–5% albumin in 250–500-ml bottles, blinding was not logistically possible. The ethics committee at each site approved the study. Written informed consent was obtained from the patient or from the legally responsible person. Randomisation was performed using computer-generated permuted blocks of 2–4 random sizes. The trial protocol including protocol deviations is provided in the Electronic Supplementary Material (ESM) 1. Before commencing enrolment, the trial was registered at http://www.anzctr.org.au (ACTRN12615000349549).

**Take-home message**

Small volume resuscitation with 20% albumin reduced resuscitation fluid requirements and minimized fluid accumulation compared with resuscitation with 4–5% albumin. Small volume resuscitation with 20% albumin did not negatively impact kidney function or other key clinical outcomes.

### Patients

We included adult (at least 18 years old) haemodynamically unstable (see ESM 2 for definitions) patients requiring an intravenous fluid bolus within 48 h of ICU admission as determined by independent treating clinicians. We excluded pregnant patients, patients in whom death was considered imminent (within 24 h), patients who refused blood products, patients with traumatic brain injury, and patients with active bleeding and/or a haemoglobin level less than 70 g/l.

### Study treatments

Patients were randomly assigned to receive fluid resuscitation with either 20% albumin or 4% (Australia) or 5% (UK) albumin from randomisation and any time during the following 48 h in ICU to achieve haemodynamic targets according to the Surviving Sepsis Campaign guidelines [19] and/or a cardiac index greater than 2.2 l/min/$m^2$ (post cardiac surgery). The volume and infusion rate of the study fluid, the use of additional resuscitation fluids (crystalloids and synthetic colloids) and the delivery of all other treatments were at the discretion of the treating clinician.

### Outcomes

The primary outcome was cumulative volume of resuscitation fluid in the first 48 h after randomisation. Secondary outcomes included volume of study fluid, cumulative fluid input, output, urine output and fluid balance, maximum norepinephrine infusion rate, maximum serum albumin level, chloride level, sodium level, creatinine level and percentage change in creatinine from baseline in the first 48 h. Exploratory clinical outcomes were duration of mechanical ventilation, commencement of renal replacement therapy (RRT) after randomisation, worsening acute kidney injury (AKI), ICU and hospital length of stay, ICU and hospital survival, rate of discharge home and long-term need for RRT. AKI was defined according to the creatinine-based KDIGO criteria [20] and worsening AKI as an increase in KDIGO stage. We used

the lowest creatinine level obtained within 6 months before ICU admission as baseline for the KDIGO classification. Missing baseline creatinine was imputed using the MDRD formula and an estimated GFR of 75 mL/min/1.73 $m^2$. Norepinephrine requirement, arterial blood pressure and central venous pressure were recorded at randomisation and hourly for 4 h thereafter to assess the early haemodynamic response. Haemoglobin and creatinine levels were recorded from available routine blood samples obtained during the same period.

#### Statistical analysis

We analysed data using STATA® version 11.2 (Stata Corp., College Station, TX, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). In the absence of any definitive data from which to base formal sample size calculations, a convenience sample of 400 patients was chosen to inform future sample size and provide preliminary evidence of safety, feasibility and efficacy.

All randomised patients, except those who withdrew consent, were included in the intention-to-treat analysis. We performed per-protocol analyses excluding 20% group patients who received 4–5% albumin (and vice versa), patients who never received the study fluid and patients who received the first fluid bolus more than 48 h after randomisation (protocol violations). Additional sensitivity analyses were performed after exclusion of patients who, in addition to the study fluid, received non-study resuscitation fluids. We also assessed the effect on the primary outcome in subgroups (operative vs. nonoperative admissions, cardiovascular surgery vs. other admissions, admission from the emergency department vs. admission from other locations, sepsis vs. no sepsis, use vs. nonuse of vasopressor at randomisation, use vs. non-use of mechanical ventilation at randomisation) with heterogeneity determined by fitting an interaction between treatment and subgroup. We compared primary and secondary outcomes using mean or median regression (with 95% CIs) depending on the underlying distribution. Heterogeneity of treatment effect in subgroups was based on an unadjusted test of interaction in a median regression model.

All data was visually assessed for normality. We used generalized linear mixed modelling with each patient treated as a random effect to assess early changes in physiological and biochemical parameters. An interaction variable (between group and time) was used in the model for comparison of changes over time between groups. As creatinine was found to be well approximated by a log-normal distribution, it was log-transformed before analysis with results presented as geometric means (95% CI). Exploratory clinical outcomes were compared using Mann–Whitney *U* or Chi-square tests. Hospital mortality and rate of discharge home censored at 90 days were presented using Kaplan–Meier curves with comparison of survival curves using a log-rank test. Multivariable logistic regression analysis was used to study the effect on mortality (details in ESM 2). A two-sided *P* value less than 0.05 was considered statistically significant.

## Results

#### Patients

In the interim analysis of the first 300 Australian patients, we found that the 20% group patients received significantly lower resuscitation volumes than 4% group patients ($P<0.001$). Since the control group in the UK received 5% albumin, a second interim analysis was performed after enrolment of all scheduled UK patients. Clear separation remained ($P<0.001$) and we therefore stopped the study. From July 2015 through February 2017, we thus randomised 330 adult patients across all sites with 159 patients assigned to the 20% group and 171 to the 4–5% group.

Six patients in the 20% group and three in the 4–5% group withdrew consent or were lost to follow-up. Therefore, we included 153 and 168 patients, respectively, in the intention-to-treat analysis (Fig. 1). Overall, 111 (72.6%) patients in the 20% group and 117 (69.6%) in the 4–5% group were admitted after major, predominantly elective surgery (Table 1). Admission after cardiac surgery was more common in the 20% group, whereas admission after gastrointestinal surgery was more common in the 4–5% group (Table S1 in ESM 2). Most baseline characteristics were similar in the two groups (Table 1). However, 4 (2.7%) and 10 (6.1%) patients were already on RRT at randomisation in the 20% group and 4–5% group, respectively. The distribution of missing baseline data was similar in the groups (Table S2 in ESM 2).

#### Co-interventions and protocol violations

Data on transfusion of blood products and the use of non-study resuscitation fluids is provided in Tables S3 and S4 in ESM 2. Overall, 39 (25.5%) and 60 (35.7%) patients received furosemide in each group. Protocol violations occurred in 9 (5.9%) 20% group patients (1 received no study fluid, 8 received 4% albumin) and 8 (4.8%) 4–5% group patients (2 received first fluid bolus after more than 48 h, 1 received no study fluid, 5 received 20% albumin).

#### Primary and secondary outcomes

The total volume of resuscitation fluid administered during the first 48 h after randomisation (primary outcome) was markedly lower in the 20% group than in the 4–5%

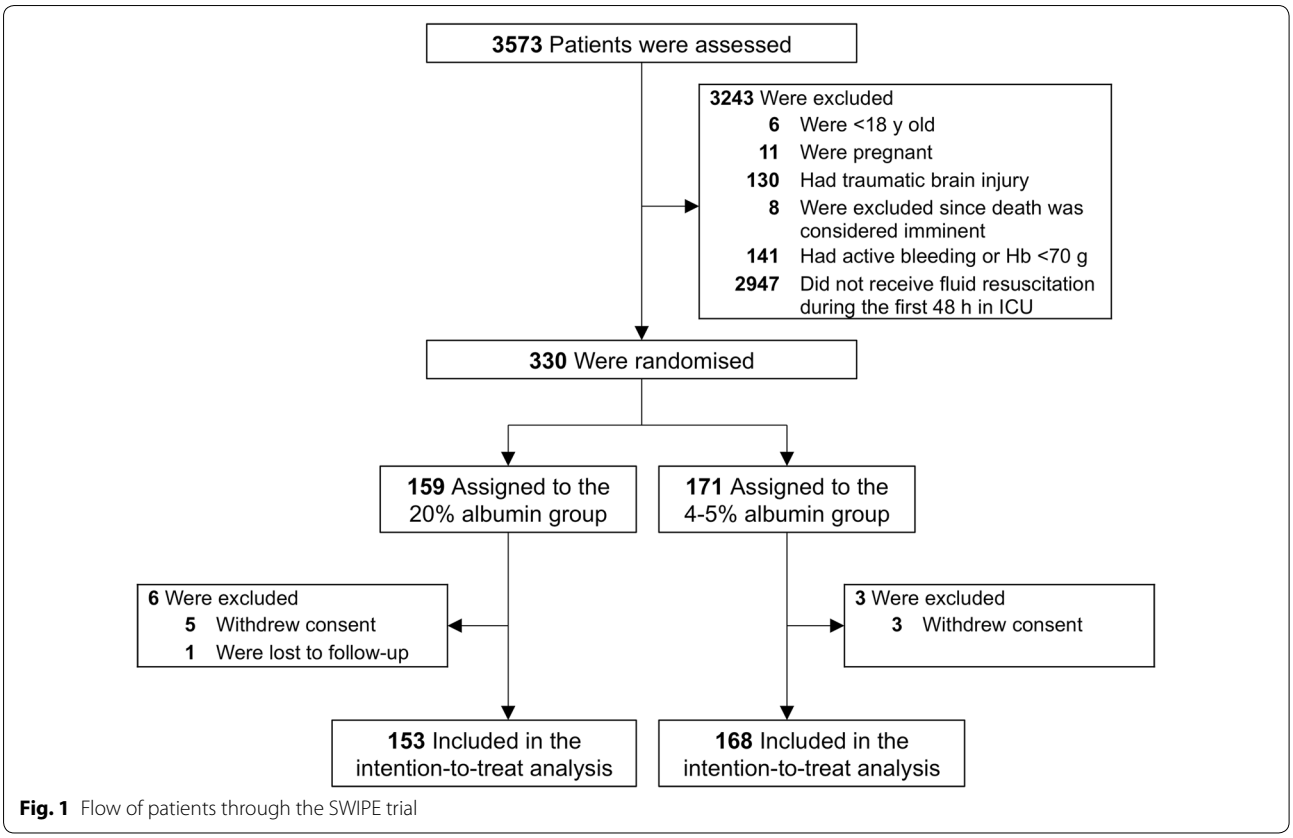


**Fig. 1** Flow of patients through the SWIPE trial

group [median difference −600 ml (95% CI −800 to −400); $P<0.001$] (Table 2). We found no significant difference in the primary outcome for the comparisons (test for heterogeneity) of operative and nonoperative patients ($P=0.33$), patients who were and those who were not admitted after cardiovascular surgery ($P=0.53$), patients with and those without sepsis ($P=0.053$), patients who were and those who were not admitted from the emergency department ($P=0.76$) and patients who received and those who did not receive vasopressor therapy on randomisation ($P=0.07$). We found a larger volume-reducing effect in the 20% group for mechanically ventilated patients ($P=0.005$) (Table S5 in ESM 2).

The volume of study fluid was lower in the 20% group [median difference −450 ml (95% CI −547 to −353); $P<0.001$]. The difference in total fluid input, output and urine output was not statistically significant. However, the 20% group had a lower cumulative fluid balance [mean difference −576 ml (95% CI −1033 to −119); $P=0.01$] (Table 2).

We observed greater albumin levels during the first 48 h in the 20% group than in the 4–5% group [mean difference 2.5 g/l (95% CI 1.2–3.8); $P<0.001$]. In contrast, chloride and sodium levels were lower in the 20% group [mean difference −1.6 mmol/l (95% CI −2.6 to −0.6); $P=0.002$ and −1.2 mmol/l (95% CI −2.1 to −0.3); $P=0.01$, respectively]. Maximum creatinine level and maximum change in creatinine from baseline were similar in the groups (Table 2). We observed similar effects on primary and secondary outcomes in the per-protocol analyses (Table S6 in ESM 2) and after excluding patients who received additional non-study resuscitation fluids (Table S7 in ESM 2).

#### Early physiological outcomes

For the initial fluid bolus, the 20% group received significantly less study fluid than the 4–5% group [median (IQR) 100 (100, 100) ml vs. 275 (250, 500) ml; $P<0.001$]. During the following 4 h, approximately half of the patients in each group received a median (IQR) of 1 (1, 2) additional fluid bolus. In addition, 77 (50.3%) 20% group patients and 83 (49.4%) 4–5% group patients received norepinephrine infusion during that time ($P=0.87$).

Systemic arterial and venous pressures increased and haemoglobin decreased in both groups during the first 4 h. We observed no significant change in creatinine in either group (Fig. 2).

#### Exploratory clinical outcomes

We observed no statistically significant difference in the duration of mechanical ventilation, RRT commenced

**Table 1 Baseline characteristics of the study patients**

| Characteristic | 20% albumin group ($n=153$) | 4–5% albumin group ($n=168$) |
|---|---|---|
| Age, median (IQR), years | 65.4 (58.4, 74.0) | 65.4 (55.5, 72.2) |
| Female sex, *n* (%) | 58 (37.9) | 67 (39.9) |
| Height, mean (SD), cm | 169 (11) | 169 (9) |
| Weight, median (IQR), kg | 74 (65, 93) | 77 (66, 90) |
| Body mass index, median (IQR), kg/m$^2$ | 27 (24, 32) | 27 (23, 31) |
| APACHE III score, median (IQR) | 50 (39, 64) | 49 (40, 69) |
| End-stage renal disease, *n* (%) | 2 (1.3) | 5 (2.9) |
| Baseline creatinine, median (IQR), μmol/l[a] | 83 (71, 108) | 88 (74, 115) |
| Baseline urea, median (IQR), mmol/l | 6.4 (4.8, 9.4) | 6.6 (4.7, 9.1) |
| Time from ICU admission to randomisation, median (IQR), h | 2.7 (0.8, 6.5) | 2.4 (0.6, 7.3) |
| Time from hospital admission to randomisation, median (IQR), h | 18 (11, 46) | 18 (10, 58) |
| Source of ICU admission, *n* (%) | | |
| Operating theatre | 107 (69.9) | 114 (67.9) |
| Emergency department | 16 (10.5) | 22 (13.1) |
| Ward | 17 (11.1) | 24 (14.3) |
| Other hospital | 13 (8.5) | 8 (4.8) |
| Operative admission diagnosis, *n* (%) | 111 (72.6) | 117 (69.6) |
| Emergency | 18/111 (16.2) | 25/117 (21.4) |
| Elective | 93/111 (83.8) | 92/117 (78.6) |
| Sepsis, *n* (%) | 17 (11.1) | 18 (10.7) |
| Albumin level on randomisation, mean (SD), g/l | 30 (8.3) | 30 (6.2) |
| Urea level on randomisation, median (IQR), mmol/l | 6.0 (4.7, 10.6) | 6.4 (4.5, 9.3) |
| Haemoglobin level on randomisation, mean (SD), g/l | 105 (18.8) | 104 (17.1) |
| Sodium level on randomisation, median (IQR), mmol/l | 138 (135, 139) | 139 (136, 141) |
| Chloride level on randomisation, median (IQR), mmol/l | 106 (103, 108) | 108 (105, 110) |
| Creatinine level on randomisation, median (IQR), μmol/l | 78 (63, 110) | 83 (66, 117) |
| Lactate on randomisation, median (IQR), mmol/l | 1.3 (1.0, 2.2) | 1.7 (1.0, 2.6) |
| Mean arterial pressure on randomisation, median (IQR), mmHg | 71 (64, 80) | 71 (64, 79) |
| Central venous pressure on randomisation, median (IQR), | 9 (6, 12) | 9 (7, 13) |
| Norepinephrine on randomisation, *n* (%) | 56 (36.6) | 64 (38.1) |
| Acute kidney injury on randomisation, *n* (%)[a] | 10 (6.8) | 14 (8.8) |
| Renal replacement therapy on randomisation, *n* (%) | 4 (2.6) | 11 (6.6) |
| Mechanical ventilation on randomisation, *n* (%) | 101 (66.0) | 111 (66.1) |

The number of missing data is provided in Table S2 in ESM 2

*APACHE* acute physiology and chronic health evaluation, *ICU* intensive care unit, *IQR* interquartile range

[a] Missing baseline creatinine was estimated from the modification of diet in renal disease equation using a GFR of 75 ml/min/1.73 m$^2$ in four patients in the 20% albumin group and five patients in the 4–5% albumin group

after randomisation, worsening AKI, or ICU or hospital lengths of stay. Overall, 149 (97.4%) patients in the 20% group and 153 (91.1%) in the 4–5% group were discharged alive from ICU ($P=0.02$). Furthermore, 143 (93.5%) and 149 (88.7%) patients in the 20% group and 4–5% group, respectively, were discharged alive from hospital ($P=0.14$) with the majority being discharged home (Table 3, Figs. S1 and S2 in ESM 2). On multivariable logistic regression analysis, we observed no independent association between 20% vs. 4–5% albumin resuscitation and ICU or hospital mortality (Tables S8 and S9 in ESM 2). One patient in the 20% group without pre-existing end-stage renal disease required RRT at 90 days.

### Specific adverse events

Hyperalbuminemia (serum albumin > 45 g/l) occurred in three patients in each group. No patient developed anaphylaxis following albumin administration.

**Table 2 Primary and secondary outcomes in the first 48 h after randomisation**

| Outcome | 20% albumin group ($n=153$) | 4–5% albumin group ($n=168$) | 20% albumin vs. 4–5% albumin (95% CI) | *P* value[a] |
|---|---|---|---|---|
| Volume of resuscitation fluid, median (IQR), ml | 300 (200, 500) | 900 (500, 1250) | − 600 (− 800 to − 400) | < 0.001 |
| Volume of study fluid, median (IQR), ml | 300 (200, 400) | 750 (500, 1250) | − 450 (− 547 to − 353) | < 0.001 |
| Total fluid input, median (IQR), ml | 3429 (2132, 4937) | 4217 (2634, 5847) | − 801 (− 1634 to 31.8) | 0.06 |
| Total fluid output, median (IQR), ml | 2995 (1850, 4409) | 3353 (2180, 4781) | − 360 (− 836 to 116) | 0.14 |
| Total urine output, median (IQR), ml | 2235 (1235, 3450) | 2407 (1429, 3580) | − 188 (− 727 to 351) | 0.49 |
| Cumulative fluid balance, mean (SD), ml | 354 (2124) | 930 (2038) | − 576 (− 1033 to − 119) | 0.01 |
| Maximum norepinephrine infusion rate, median (IQR), µg/min | 2 (0, 6) | 4 (0, 10) | − 2 (− 5 to 1) | 0.19 |
| Maximum albumin level, mean (SD), g/l | 35 (6.2) | 32 (5.4) | 2.5 (1.2–3.8) | < 0.001 |
| Maximum chloride level, mean (SD), mmol/l | 106 (4.5) | 107 (4.7) | − 1.6 (− 2.6 to − 0.6) | 0.002 |
| Maximum sodium level, mean (SD), mmol/l | 140 (3.8) | 141 (4.4) | − 1.2 (− 2.1 to − 0.3) | 0.01 |
| Maximum creatinine level, median (IQR), µmol/l | 95 (75, 132) | 101 (77, 153) | − 6 (− 17 to 5) | 0.30 |
| Maximum change in creatinine from baseline, median (IQR), % | 10 (− 2, 35) | 11 (− 7, 34) | − 1 (− 9 to 8) | 0.83 |

*IQR* interquartile range

[a] *P* value derived using mean or median regression

## Discussion

### Key findings

We conducted a randomised controlled trial to assess resuscitation fluid requirements, fluid balance and the physiological and biochemical response of patients resuscitated with 20% or 4–5% albumin solutions during the 48 h after initiation of fluid resuscitation in ICU. Patients in the 20% group received two-thirds less resuscitation fluid and had a significantly lower cumulative fluid balance at 48 h. We also found that norepinephrine requirement and the early physiological responses were similar between groups. In contrast, serum albumin levels were greater and chloride and sodium concentrations lower in patients receiving 20% albumin. Finally, resuscitation with 20% albumin did not negatively impact kidney function or other key clinical outcomes.

### Relationship with previous studies

Compared with our study, resuscitation volumes were greater in previous colloid trials [2, 3, 21]. Greater illness severity, a higher proportion of septic patients in previous trials and inclusion of cardiac surgery patients in our trial likely explain this difference. Fluid resuscitation outside the ICU (not recorded in our study) may also contribute to the differences. However, similar to our patients, in a recent study of patients with septic shock, the mean volume of resuscitation fluid administered after initial resuscitation was 750 ml [22]. Despite already limited fluid exposure in the 4–5% group, the amount of resuscitation fluid and the cumulative fluid balance were further reduced in our patients assigned to receive 20% albumin. Such small volume resuscitation was not associated with any signal of harm. In accord with a previous study in patients with septic shock [23], our data suggest that a volume-restrictive resuscitation approach may also be safe in non-septic patients admitted after major surgery.

The early haemodynamic response and degree of haemodilution after the initial bolus of 100 ml of 20% albumin appeared equivalent to that of the initial bolus of 275 ml of 4–5% albumin in our study. This finding supports previous experimental data suggesting that the intravascular volume effect of 20% albumin is approximately twice the volume effect of 4–5% albumin [4, 6, 8, 9]. Attenuated fluid extravasation with 20% albumin may explain this finding [8]. For example, in the 4 h following infusion of 20% albumin in septic patients, an 8% reduction in haematocrit was observed corresponding to a volume expanding effect of approximately twice the infused volume [9]. This is consistent with our finding of a mean reduction in haematocrit of 9% at 4 h.

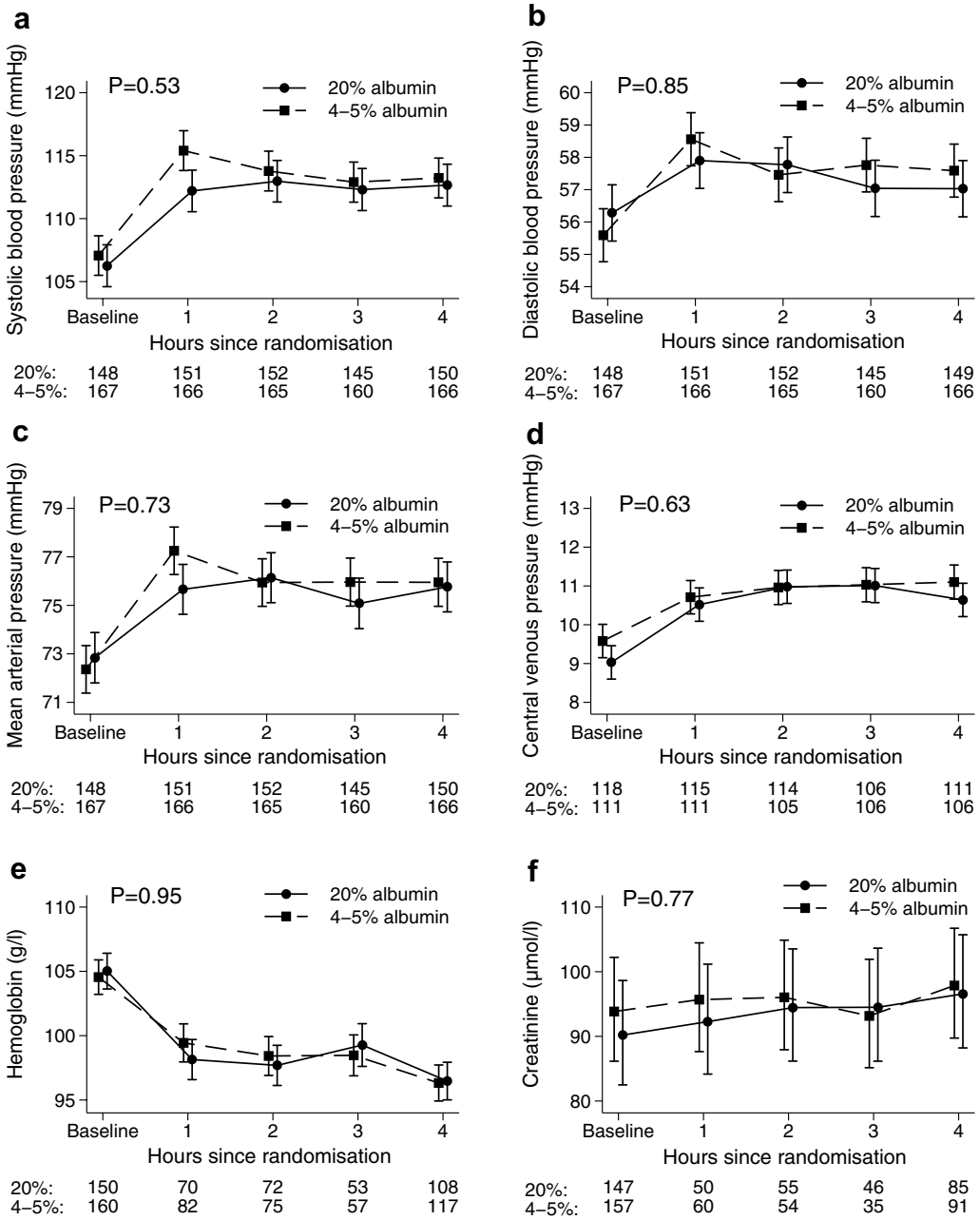


**Fig. 2** Systolic blood pressure (**a**), diastolic blood pressure (**b**), mean arterial pressure (**c**), central venous pressure (**d**), haemoglobin (**e**) and creatinine (**f**) at the time of randomisation (baseline) and during the first 4 h after randomisation in patients receiving 20% albumin (circles) and 4–5% albumin (squares), respectively. Data are means with SEM (**a**–**e**) or geometric means with 95% CI (**f**). The *P* values for the between-group comparison represent the interaction between group and time in the repeated-measures generalized linear mixed model. The number of data points at each time point is shown beneath the graphs

Australian 20% albumin solutions have a lower sodium (40–100 mmol/l) and chloride (approximately 19 mmol/l) concentration than 4–5% albumin solutions (approximate sodium concentration 140 mmol/l; approximate chloride concentration 128 mmol/l) [24]. In patients with severe sepsis/septic shock, administration of 4% albumin (median 500 ml) post-resuscitation significantly increased serum chloride levels without affecting serum sodium levels [25]. In contrast, in critically ill hypoalbuminemic patients, rapid infusion of

**Table 3 Exploratory clinical outcomes**

| Outcome | 20% albumin group ($n=153$) | 4–5% albumin group ($n=168$) | Risk ratio or absolute difference (95% CI)[b] | *P* value |
|---|---|---|---|---|
| Mechanical ventilation, *n* (%) | 112 (73.2) | 118 (70.2) | 1.04 (0.91–1.20) | 0.56 |
| Mechanical ventilation, median (IQR), h | 12.0 (7.6, 33.1) | 15.3 (7.7, 58.1) | −3.0 (−6.9 to 0.8) | 0.13 |
| Renal replacement therapy commenced after randomisation, *n* (%) | 5 (3.3) | 7 (4.2) | 0.78 (0.25–2.42) | 0.67 |
| Worsening acute kidney injury, *n* (%)[a] | 19/148 (12.8%) | 26/159 (16.4%) | 0.79 (0.45–1.36) | 0.38 |
| ICU length of stay, median (IQR), days | 2.6 (1.1, 5.0) | 2.8 (1.6, 4.8) | −0.2 (−1.5 to 1.1) | 0.62 |
| Hospital length of stay, median (IQR), days | 11 (8, 18) | 11 (7, 22) | −0.5 (−2.9 to 2.0) | 0.53 |
| Discharged alive from ICU, *n* (%) | 149 (97.4) | 153 (91.1) | 1.07 (1.01–1.13) | 0.02 |
| Discharged alive from hospital, *n* (%) | 143 (93.5) | 149 (88.7) | 1.05 (0.98–1.13) | 0.14 |
| Hospital discharge destination in survivors, *n* (%) | | | | 0.65 |
| Home | 115/143 (80.4) | 120/149 (80.5) | 1.00 (0.89–1.12) | |
| Other hospital | 25/143 (17.5) | 25/149 (16.8) | 1.04 (0.63–1.73) | |
| Institution for advanced care | 2/143 (1.4) | 4/149 (2.7) | 0.52 (0.10–2.80) | |
| Still in same hospital at 90 days | 1/143 (0.7) | 0 | – | |

*IQR* interquartile range, *ICU* intensive care unit

[a] Defined as a 1-unit increase in the creatinine-based KDIGO acute kidney injury criteria or commencement of renal replacement therapy

[b] Absolute differences in mechanical ventilation duration, ICU length of stay and hospital length of stay are obtained using median regression. For all other measures, risk ratios are given

20% albumin significantly reduced serum chloride levels without changing serum sodium levels [26]. Similarly, we observed significantly greater serum chloride levels during the first 48 h in patients resuscitated with 4–5% albumin than in patients receiving 20% albumin. However, in contrast to previous studies, we also found greater sodium levels in the 4–5% group. Administration of chloride-rich fluids may impair GFR via tubuloglomerular feedback activation [27]. This idea was supported by observational data [28, 29] but with conflicting results in large cluster-randomised trials [30–33]. If avoidance of chloride-rich fluids is desirable, 20% albumin has the lowest chloride concentration of any fluid on the market. We found no difference in peak creatinine levels, peak change in creatinine from baseline, post-randomisation need for RRT or worsening AKI despite greater sodium chloride exposure in the 4–5% group.

Plasma oncotic pressure counteracts glomerular hydraulic pressure and may decrease GFR. A negative impact of hyperoncotic solutions, such as 20% albumin, on kidney function has been suggested [16]. However, concerns about increasing the glomerular capillary oncotic pressure with albumin may not be justified as novel findings suggest that significant glomerular albumin filtration occurs [34]. Indeed, treatment of hypoalbuminemia with 20% albumin did not significantly increase the occurrence rate of AKI or RRT requirements in septic patients [3]. In contrast, preoperative administration of 20% albumin before coronary artery bypass surgery reduced postoperative AKI incidence [35]. Our findings that greater albumin exposure (median 60 g in the 20% group vs. 30–40 g in the 4–5% group) did not impact the early rise in creatinine or AKI risk suggest that concerns about a negative renal impact from 20% albumin resuscitation may be unwarranted.

Finally, we observed reduced ICU mortality in patients receiving 20% albumin. This finding may represent a type 1 error. Imbalances in some baseline characteristics, a non-significant effect on ICU mortality in adjusted analysis, and the smaller between-group difference in hospital mortality emphasize the need to view the ICU mortality finding with caution.

### Study implications

Our findings imply that small volume resuscitation with 20% albumin is feasible and produces a similar early haemodynamic response as larger volume resuscitation with 4–5% albumin. Moreover, they imply that resuscitation with 20% albumin is likely safe and may reduce early resuscitation fluid administration requirements and cumulative fluid balance. Finally, they support continued assessment of small volume resuscitation with

20% albumin in larger randomised trials of ICU patients requiring fluid bolus therapy as determined by the treating clinician.

### Strengths and weaknesses

Our study has several strengths. It is a randomised trial conducted at three centres in two countries comparing two cohorts with similar characteristics at baseline, indicating successful randomisation and increasing both internal and external validity. Our study provides a detailed assessment of the early haemodynamic and biochemical responses as well as the effect on fluid accumulation over 2 days, thus providing useful predictive information for clinicians. Finally, we observed consistent results in per-protocol and sensitivity analyses, which lends robustness to our findings.

Our study has some limitations. It is unblinded and therefore subject to treatment bias; the clinician's perception that 20% albumin has a greater volume expanding effect may have reduced the administration of this and other fluids. However, one-third of the initial fluid bolus volume given in the 20% group as compared with the 4–5% group produced a similar early haemodynamic response. We lack fluid data beyond 48 h. However, the median ICU length of stay was only 2.5 days after randomisation. The trial was stopped after two interim analyses, which may have overestimated the primary outcome effect. However, since our primary outcome carries a $P<0.001$, the loss of alpha associated with two interim analyses would be unlikely to affect the significance of this finding. We enrolled only a few septic patients and the generalizability of our study findings to such patients is therefore limited. Finally, we did not compare 20% albumin-based small volume resuscitation with crystalloid resuscitation, which is standard practice in some centres. However, it seems likely, given the Saline vs. Albumin Fluid Evaluation (SAFE) trial results comparing saline with 4% albumin [2], that such a comparison would have led to an even greater separation in resuscitation fluid administration and fluid balance in favour of 20% albumin.

## Conclusions

In our cohort of surgical and medical ICU patients, small volume resuscitation with 20% albumin reduced resuscitation fluid volume requirements and cumulative fluid balance compared with resuscitation with 4–5% albumin, with no demonstrable evidence of harm. These findings support the case for further investigation of small volume resuscitation in larger randomised trials.

**Electronic supplementary material**

The online version of this article (https://doi.org/10.1007/s00134-018-5253-2) contains supplementary material, which is available to authorized users.

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**Compliance with ethical standards**

**Conflicts of interest**

The authors declare that they have no conflict of interest.

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