RESEARCH ARTICLE

A Prospective Observational Study of Rational Fluid Therapy in Asian Intensive Care Units: Another Puzzle Piece in Fluid Therapy

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Abstract

Introduction: Fluid therapy in critically ill patients, especially timing and fluid choice, is controversial. Previous randomized trials produced conflicting results. This observational study evaluated the effect of colloid use on 90-day mortality and acute kidney injury (RIFLE F) within the Rational Fluid Therapy in Asia (RaFTA) registry in intensive care units.

Materials and methods: RaFTA is a prospective, observational study in Asian intensive care unit (ICU) patients focusing on fluid therapy and related outcomes. Logistic regression was performed to identify risk factors for increased 90-day mortality and acute kidney injury (AKI).

Results: Twenty-four study centers joined the RaFTA registry and collected 3,187 patient data sets from November 2011 to September 2012. A follow-up was done 90 days after ICU admission. For 90-day mortality, significant risk factors in the overall population were sepsis at admission (OR 2.185 [1.799; 2.654], $p < 0.001$), cumulative fluid balance (OR 1.032 [1.018; 1.047], $p < 0.001$), and the use of vasopressors (OR 3.409 [2.694; 4.312], $p < 0.001$). The use of colloids was associated with a reduced risk of 90-day mortality (OR 0.655 [0.478; 0.900], $p = 0.009$). The initial colloid dose was not associated with an increased risk for AKI (OR 1.094 [0.754; 1.588], $p = 0.635$).

Conclusion: RaFTA adds the important finding that colloid use was not associated with increased 90-day mortality or AKI after adjustment for baseline patient condition.

Clinical significance: Early resuscitation with colloids showed potential mortality benefit in the present analysis. Elucidating these findings may be an approach for future research.

Keywords: Acute kidney injury, Colloids, Critical illness, Crystalloids, Fluid therapy, Hydroxyethyl starch.

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Introduction

Fluid therapy in critically ill patients is an important aspect of care that is currently under debate. Especially the choice of fluid remains highly controversial for this patient population.[1–6] Most importantly, colloid use in critically ill patients has been challenged by several studies and meta-analyses during the last years. Many of them reported increased mortality and acute kidney injury (AKI) especially with hydroxyethyl starch.[7–11]

However, there have been some concerns about studies that were showing negative outcomes associated with colloids, mainly about the largest three trials VISEP,[7] 6S,[8] and CHEST.[11] CHEST showed no mortality differences for colloids *vs* crystalloids,[12] while VISEP and 6S randomized patients 24 hours after diagnosis of septic shock. At this time, most of the patients were hemodynamically stable and a substantial number of them had received HES for stabilization before randomization.[12–14] Furthermore, colloids were given for prolonged periods up to 28 days, which is usually not the case in clinical practice.

In contrast, the CRISTAL trial[15] randomized patients early and did not mandate the use of colloids by the protocol for a prolonged period. The results of this trial were significantly reduced 90-day mortality and no increased renal risk associated with colloids. Furthermore, the observational study RaFTinG[16] collected data from regular clinical routine in German intensive care units (ICUs) and could not identify any relevant risk associated with colloids. To add

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more data on the use of colloids in routine clinical practice, we set up a clinical registry entitled Rational Fluid Therapy in Asia (RaFTA). The main focus of this registry was to evaluate the demographic, diagnostic, and therapeutic characteristics of unselected Asian ICU patients with a focus on fluid therapy and related outcomes. Due to the declining use of colloids in ICUs worldwide, these data may be an important source for exploratory research.

For the present analysis, we first searched for safety signals related to colloid and crystalloid treatment. Second, we looked for associations that may point toward an explanation for the inconsistencies in the outcome of previous studies to develop hypotheses for future research.

Materials and Methods

The RaFTA registry aimed to evaluate the demographic, diagnostic, and therapeutic characteristics of unselected ICU patients with a focus on fluid and volume therapy.

Ethical Considerations

The protocol has been approved as an extension of the RaFTinG registry[16] and written informed consent was obtained from patients or their representatives to allow contact for follow-up. Patients or representatives who were not able to decide on their consent at the time of inclusion were reassessed for consent later.

Study Population

All adult patients with an indication for fluid therapy and a presumed length of ICU stay >24 hours were considered for inclusion into the registry. The indication for fluid therapy was judged by the attending physician. Exclusion criteria were psychiatric disorders, reasonable doubt regarding the respective patient's discernment, and institutionalization upon court or other official orders. Inclusion started in November 2011 and was finished in September 2012.

Study Protocol

All diagnostic and therapeutic decisions were left to the discretion of the attending physician according to local standards. All records that have been documented in the study database were part of the centers' documentation routine.

Documentation started at ICU admission and was completed at ICU discharge. For each patient, basic biometrical data, diagnoses upon admission, hemodynamic, laboratory parameters, and severity scores [Acute Physiology And Chronic Health Evaluation, APACHE II;[17] Simplified Acute Physiology Score, SAPS II;[18] Sequential Organ Failure Assessment score, SOFA;[19,20] Therapeutic Intervention Scoring System, TISS[21]] were documented. On each consecutive day during ICU stay, new diagnoses, hemodynamic and laboratory variables, fluid balance, and therapeutic interventions were assessed. If the patient survived the ICU stay, he or she was contacted by mail or phone to retrieve his or her survival status at 90 days after ICU admission.

Data Collection

Data entry was made in electronic forms. Data validity was ensured by automatic inquiries for values outside of pre-specified limits. Also, all data were continuously checked for formal and content-related errors. In the case of missing and inconsistent data, the centers were asked for re-assessment.

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Conflict of interest: None

Outcome

The outcome parameters of main interest were selected for safety evaluation: 90-day mortality (death within 90 days after first ICU admission) and AKI ("failure" according to RIFLE).[22] During the creation of the study protocol, RIFLE was the most recent classification to stratify the severity of AKI. Also, we considered RIFLE more appropriate than AKIN to identify AKI because it relies less on the initiation of renal replacement therapy (RRT). Given the different healthcare systems in the participating countries, we think RRT initiation may have been influenced substantially by the different healthcare systems and national therapeutic approaches. Moreover, the use of RRT was analyzed for the sake of completeness, although the indication for RRT was based on the judgment of the individual physician.

To assess the impact of type and dosage of colloids on the respective outcome of interest, patients were stratified as having received (i) crystalloids and colloids or (ii) exclusively crystalloids during ICU stay. Similar to the CRISTAL trial, we did not differentiate between colloids because we aimed at pragmatic exploration of two different therapeutic strategies (colloid vs non-colloid based approaches).

Statistical Analysis

Data are presented as median (25th; 75th percentiles) for ordinal and continuous numeric variables. Categorical variables are given as percentages, if not otherwise specified. Ninety-day survival, AKI, and the use of RRT were analyzed by logistic regression with the following cofactors and covariables: fluid balance, sepsis, and chronic kidney disease at admission and the number of days of substantial vasopressor use which are well-known risk factors for

mortality and AKI.[23,24] Substantial vasopressor use was defined as any dosage >0.6 mg/hour (corresponding to ≥0.1 µg/kg/minute for patients weighing 100 kg or less), as this cut-off has been established in the literature.[16,25–27] Furthermore, it was obvious from the raw data that the severity of illness at admission correlated with the use of colloids. Thus, we included the first TISS score, which was the score most often documented by the centers, as a measure of severity of illness for the multivariate model. Gender was included in the model because male subjects dominated in the registry and thus might have introduced bias. To assess colloid use we chose the colloid volume on the first day of colloid infusion for two reasons: first, cumulative or the daily average dose may induce marked variance in patients with long ICU stay but only occasional colloid infusion. Second, a fluid regimen for hemodynamic stabilization should focus on the very first hours of the hypovolemic condition. Therefore, the initial colloid dose a patient receives would be close to the total dose received and would represent best the use of a colloid for initial hemodynamic stabilization.

Only patients with data for all covariables were included in the analyses. For 90-day mortality, the effect of patients lost to follow-up was evaluated by a best/worst-case analysis with all patients lost to follow-up set to "alive" or "having died on the day after ICU discharge". Furthermore, we did a stratification of patients according to the timing of the initial colloid use. We assumed that patients receiving colloids on their first days of ICU stay are most likely to receive volume therapy based on a fluid therapy protocol and those who received colloids for the first time later during their ICU stay are more likely to belong to a group of patients with protracted and difficult-to-control disease. Thus, we exploratively compared three subgroups of patients for 90-day mortality: patients receiving their first colloid dose on day 1 of ICU stay, patients receiving their initial colloid dose on day 1 or 2 of ICU stay, and patients receiving their initial colloid dose on day 3 or later. We calculated the multivariate odds ratios for the three groups because a targeted volume therapy for initial hemodynamic instability can be expected to be performed on day 1 or day 2 in the ICU. As the results of the analysis for patients treated on day 1 and those treated on day 1 and day 2 have been analyzed independently, this process did not influence the mathematical power of the other analysis. This stratification also aimed to find out whether the risk factors stay consistent within different therapeutic subgroups of the population.

Results

Recruitment

Twenty-four centers joined the RaFTA registry, collecting data of 3,187 patients (India: 18 centers, 2,404 patients; Malaysia: 4 centers, 394 patients; Taiwan: 2 centers, 389 patients). One hundred and forty-nine patients were lost to follow-up (follow-up rate of 95.3%). Two thousand six hundred and twenty-one patients had records for each variable required for multivariate analysis of AKI and use of RRT and therefore were considered valid for this analysis (validity rate 82.2%) (Flowchart 1).

Patient Characteristics and Fluid Therapy

Patient characteristics at admission differed among the national subgroups (Table 1): patients from Malaysia were most critically ill in terms of sepsis, mechanical ventilation, or chronic kidney disease, while patients from Taiwan were the oldest and had the highest incidence of cancer. Thus, overall and national subgroup analysis was done in parallel.

Most patients received colloids during their first days of ICU stay (Fig. 1A). The administered median dose was 0.25 [0.10; 0.50] liters at the first day of ICU stay and decreased to about 0.1 liter per day later on (e.g., day 2: 0.12 [0.10; 0.50] liter, day 3: 0.10 [0.10; 0.33] liter). Administration modes differed between countries as shown in Figure 1B: first, the number of colloid receivers was about 60% in Malaysia and Taiwan but only 24% in India. Second, colloid dosing and the underlying fluid regimen were different as indicated by fluid balance and colloid dose in Table 2. The use of different colloids is shown in Figure 1B. More than one colloid was used in 21% of colloid receivers, with 32, 29, and 13% in Malaysia, Taiwan, and India, respectively. Fluid balance substantially differed between colloid receivers and non-receivers, which especially in the Indian subgroup goes in parallel with the severity of the patients' condition as indicated by the first TISS score.

Outcome

We analyzed 90-day mortality, AKI, and the use of RRT to evaluate outcomes and risks associated with the initial colloid dose as

Flowchart 1: Patient flow

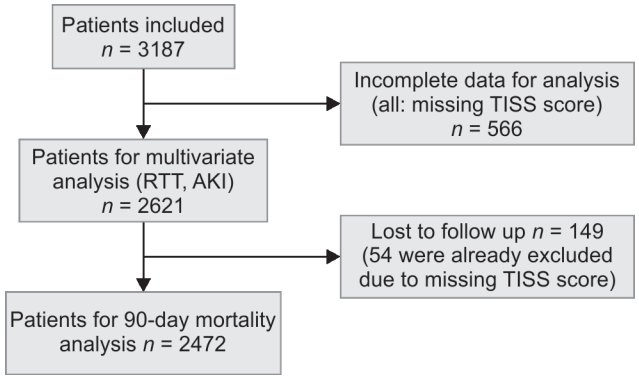
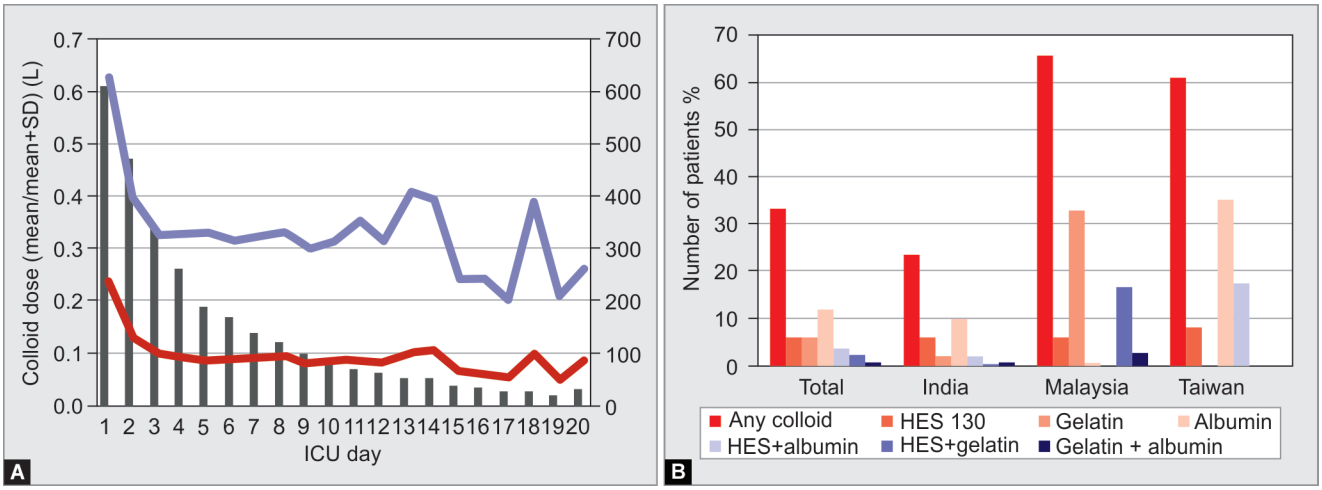


Table 1: Patient characteristics at baseline

	Total (n = 3,187)	*India (n = 2,404)*	*Malaysia (n = 394)*	*Taiwan (n = 389)*
Gender (*N*, % male)	2,066 (65%)	1,564 (65%)	257 (65%)	245 (63%)
Age on admission; years (median, IQR)	56 (45; 67)	55 (45; 65)	52 (36; 65)	70 (57; 80)
ICU length of stay; days (median, IQR)	3 (2; 6)	3 (2; 5)	4 (2; 8.75)	6 (3; 13)
Sepsis on admission (*N*, %)	842 (26%)	675 (28%)	156 (40%)	11 (3%)
Chronic kidney disease on admission (*N*, %)	649 (20%)	483 (20%)	133 (34%)	33 (8%)
Ventilated (*N*, %)	988 (31%)	692 (29%)	231 (59%)	65 (17%)
Cancer (*N*, %)	510 (16%)	322 (13%)	39 (10%)	149 (38%)
First TISS score (median, IQR)	18 (13; 26)	17 (9; 25)	22 (18; 26)	22 (17; 29)

ICU, intensive care unit; IQR, interquartile range; TISS, therapeutic intervention scoring system



Figs 1A and B: (A) Mean colloid dose (red line) + standard deviation (blue line) and the number of patients receiving colloids; (B) Percentages of patients receiving colloids and different types of colloids. SD, standard deviation; HES, hydroxyethyl starch

described in the Materials and methods section. Raw data for these analyses are shown in Table 2.

90-day Mortality

Significant risk factors in the overall population (Table 3) were sepsis at admission (OR 2.185 [1.799; 2.654], $p < 0.001$), cumulative fluid balance (1.032 [1.018; 1.047], $p < 0.001$), and the use of vasopressors (OR 3.409 [2.694; 4.312], $p < 0.001$). The initial use of colloids on day 1 was associated with a reduced risk of mortality (OR 0.655 [0.478; 0.900], $p = 0.009$). The results of best/worst-case analyses assuming survival or death of patients lost to follow-up were very similar to the regular analyses (Fig. 2).

Acute Kidney Injury

For AKI defined as RIFLE F score, independent risk factors were sepsis at admission (OR 1.387 [1.091; 1.763], $p = 0.008$), chronic kidney disease at admission (OR 10.860 [8.549; 13.795], $p < 0.001$), first TISS score (OR 1.420 [1.256; 1.605], $p < 0.001$), cumulative fluid balance (OR 1.032 [1.018; 1.047], $p < 0.001$), and vasopressor use (OR 1.981 [1.488; 2.639], $p < 0.001$). In the Indian subgroup, male gender was a statistically significant protective factor (OR 0.735 [0.559; 0.967], $p = 0.028$). The overall trends were similar in the national subgroups, although not all effects were significant. The initial colloid dose is not associated with an increased risk for AKI neither in the total study population (OR 1.094 [0.754; 1.588], $p = 0.635$) nor the national subcohorts (Table 4).

Renal Replacement Therapy

For the use of RRT, significant risk factors were sepsis at admission (OR 1.454 [1.087; 1.945], $p = 0.012$), chronic kidney disease at admission (OR 8.056 [6.025; 10.777], $p < 0.001$), first TISS score (OR 1.647 [1.404; 1.932], $p < 0.001$), and vasopressor use (OR 2.649 [1.949; 3.600], $p < 0.001$). These effects were similar in all countries. Again, initial colloid use was not associated with a significant increase in the use of RRT (Table 5).

Exploratory Analyses

The exploratory analyses (Fig. 3) showed that most of the risk factors for mortality were not dependent on the time of first colloid use. In contrast, the association of initial colloid dose and mortality was dependent on the time of first colloid use. In the overall population, early colloid use (day 1 of ICU stay) was associated with a significantly lower risk for 90-day mortality (OR 0.552 [0.385; 0.792]; $p = 0.001$) as was initial colloid dose on day 1 or day 1 + 2 (OR 0.561 [0.357; 0.880]; $p = 0.012$). In contrast, for late colloid receivers (day 3 or later), there was no significant association between mortality and colloid use (OR 1.399 [0.629; 3.113]; $p = 0.410$).

The only univariate difference among the covariates of the logistic regression between the early and late colloid subcohorts was that late colloid receivers had a larger cumulative fluid balance (4.6 [0.9; 10.8] liters *vs* 2.3 [0.2; 5.5] liters).

Discussion

RaFTA showed that colloid use was not associated with an increased risk of mortality or AKI but might even be correlated with a survival benefit in the Asian ICU population. Subgroup analyses in patients receiving colloids early (day 1 or 2) or late during their ICU stay (day 3 or later) suggest that timing of the first colloid is associated with outcome and might affect possible benefit or harm of the specific drug. In our analysis, colloids were not associated with increased mortality or AKI in ICU patients if they were provided early after ICU admission.

The analysis of RaFTA also suggests that arguments challenging the results of the previous large trials in sepsis,[12–14] 6S,[8] and VISEP,[7] maybe worth considering in the current debate. It showed that patients in need of volume therapy >2 days after ICU admission represent a subpopulation in which colloid treatment does not appear to be beneficial. Taking into account this idea and the fact that 6S and VISEP randomized their patients 24 hours after ICU admission, we conclude that the adverse outcome associated with colloids in these studies may not only be an effect of the study drug. Our results might be interpreted as support of the CRISTAL protocol and suggest that colloids might be beneficial for early resuscitation in individual patients. The median volume of colloid administered was the highest on day 1 with 250 mL and declined to 100 mL in the following days. This reflects that many patients did not receive full units of the respective colloid. Thus, it appears that colloids have been used for a fluid challenge in many cases. Nevertheless, it has been shown that even such low amounts of colloids increase stroke volume in hypovolemic, fluid responsive patients.[23,28]

Table 2: Raw data

Group	*Total (n = 3,187)*		*India (n = 2,404)*		*Malaysia (n = 394)*		*Taiwan (n = 389)*	
Subgroup	*Colloid*	*No colloid*	*Colloid*	*No colloid*	*Colloid*	*No colloid*	*Colloid*	*No colloid*
Number of patients (*N*, % of group)	1,062 (33%)	2,125 (67%)	566 (24%)	1,838 (76%)	259 (66%)	135 (34%)	237 (61%)	152 (39%)
Sepsis at admission (*N*, % of subgroup colloid/no colloid)	317 (30%)	525 (25%)	213 (38%)	462 (25%)	100 (39%)	56 (41%)	4 (2%)	7 (5%)
Chronic kidney disease at admission (*N*, % of subgroup colloid/no colloid)	248 (23%)	401 (19%)	151 (27%)	332 (18%)	77 (30%)	56 (41%)	20 (8%)	13 (9%)
First TISS score (median, IQR)	23 (17; 30)	17 (9; 22)	22 (14.5; 33)	17 (9; 25)	23 (18; 29)	22 (13; 25)	25 (21; 30)	20 (13; 22)
Cumulative fluid balance, l (median, IQR)	2.77 (0.35; 6.57)	1.09 (0; 3.24)	4.03 (1.52; 9.01)	1.65 (0.22; 4.40)	1.49 (0; 4.59)	0.19 (−0.81; 0.92)	0.67 (−1.19; 4.09)	0.77 (−0.43; 2.45)
Initial colloid dose, l (median, IQR)	0.24 (0.10; 0.50)		0.20 (0.10; 0.50)		0.25 (0.20; 0.50)		0.10 (0.10; 0.50)	
Vasopressor use (>0.6 mg/hour) (*N*, % of subgroup colloid/no colloid)	381 (36%)	293 (14%)	242 (43%)	265 (14%)	109 (42%)	20 (15%)	30 (13%)	8 (5%)
Deaths (*N*, % of subgroup colloid/no colloid)	443 (42%)	798 (38%)	293 (52%)	733 (40%)	93 (36%)	31 (23%)	57 (24%)	34 (22%)
RIFLE failure during ICU stay and follow-up (*N*, % of subgroup colloid/no colloid)	285 (27%)	371 (17%)	154 (27%)	304 (17%)	83 (32%)	50 (37%)	48 (20%)	17 (11%)
Renal replacement therapy during ICU stay (*N*, % of subgroup colloid/no colloid)	169 (16%)	173 (8%)	84 (15%)	137 (7%)	60 (23%)	32 (24%)	25 (11%)	4 (3%)

ICU, intensive care unit; IQR, interquartile range; TISS, therapeutic intervention scoring system

Table 3: Odds ratios for 90-day mortality in the total study population and national subgroups

	Total (n = 2,472)				*India (n = 1,836)*			
Effects	*Sig.*	*OR*		*95% CI*	*Sig.*	*OR*		*95% CI*
Gender (M vs F)	0.765	1.027	0.861	1.225	0.721	0.964	0.786	1.181
Sepsis at admission (y/n)	<0.001	2.185	1.799	2.654	<0.001	2.121	1.699	2.647
Chronic kidney disease at admission (y/n)	0.185	1.158	0.932	1.440	0.586	1.072	0.834	1.379
First therapeutic intervention scoring system	0.574	1.026	0.937	1.124	0.013	1.143	1.028	1.271
Cumulative fluid balance	<0.001	1.032	1.018	1.047	0.548	1.004	0.991	1.018
Initial colloid dose (first day with colloids)	0.009	0.655	0.478	0.900	0.196	1.412	0.837	2.380
Vasopressors (y/n)	<0.001	3.409	2.694	4.312	<0.001	2.933	2.221	3.874
	Malaysia (n = 294)				*Taiwan (n = 342)*			
Effects	*Sig.*	*OR*		*95% CI*	*Sig.*	*OR*		*95% CI*
Gender (M vs F)	0.812	0.930	0.512	1.689	0.296	1.366	0.761	2.451
Sepsis at admission (y/n)	0.125	1.584	0.881	2.848	0.159	2.778	0.670	11.514
Chronic kidney disease at admission (y/n)	0.014	2.131	1.168	3.887	0.539	0.734	0.274	1.967
First therapeutic intervention scoring system	0.438	1.165	0.791	1.716	0.126	1.284	0.932	1.768
Cumulative fluid balance	0.016	1.059	1.011	1.109	<0.001	1.211	1.124	1.305
Initial colloid dose (first day with colloids)	0.990	0.996	0.550	1.805	0.087	0.458	0.187	1.121
Vasopressors (y/n)	<0.001	3.600	1.907	6.798	0.001	5.024	1.912	13.204

y, yes; n, no; M, male; F, female

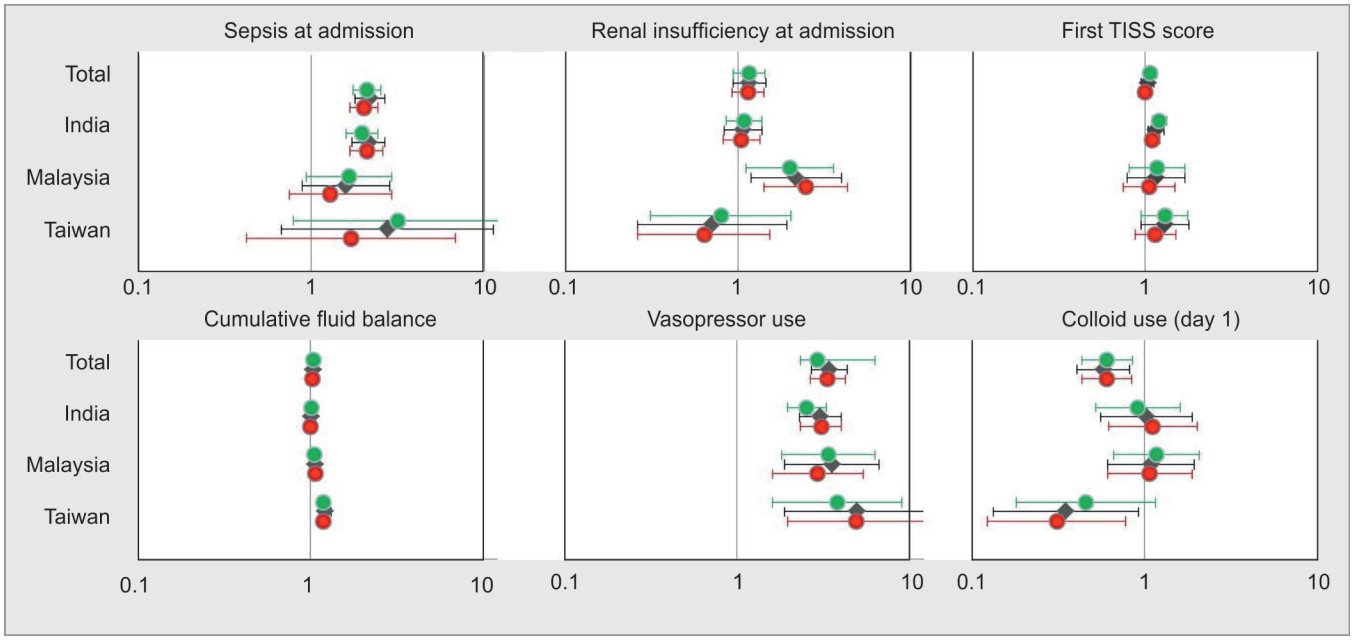


Fig. 2: Odds ratios for 90-day mortality in the total study population and national subgroups in a best/worst-case scenario [all patients with missing mortality data were taken into account as dead (red) or alive (green) during 90-day follow-up]

For 90-day mortality, the results were similar in the national subcohorts, although the survival benefit associated with colloids was not significant in these subpopulations. The difference between subgroups and the total population may be a result of lower patient numbers in the subgroups from Malaysia and Taiwan.

Interestingly, in the exploratory investigated subgroups with early or late first colloid use all odds except for the one for colloid use seem to be stable. This might indicate that timing or other unknown aspects of colloid use may affect the outcome. The larger fluid balance in colloid receivers again indicates that benefit or harm associated with colloids might be a matter of the underlying indication of their use. A similar result has also been observed for the incidence of AKI in burn patients.[29] In this study, colloid use in the first 12 hours was associated with a trend toward a lower incidence of AKI.

The most important limitation of our study is the inclusion of different national subcohorts with different patient populations and possibly different therapeutic approaches. Therefore, we did a pooled analysis as well as an analysis of the national subgroups. Taking into account the different numbers of patients in the national cohorts, we found no conflicting results among the total cohort and subcohorts. Furthermore, several subgroup analyses showed consistent and clinically reasonable results, suggesting that the chosen models were appropriate.

We are aware that we can only make informed guesses why the effect on the outcome of late colloid use seems to differ from early use. We assume that this might be due to substantial changes in the patients' condition that could not be covered by our analysis, e.g., patients with worsening shock or failure of resuscitation. However, our approach was exploratory and thus, RaFTA may provide some puzzle pieces with real-life data and suggest topics for future research. Such a topic might be to elucidate which patients are at risk for adverse outcomes after late colloid use.

Two additional aspects might also contribute to the explanation of time-dependency:

First, the choice of the initial daily colloid dose might be questioned as an indicator of rational volume therapy. However, in a rational resuscitation concept of critically ill patients, colloids will be indicated (if at all) early. Thus, the first-day colloid dose may reflect initial fluid requirements. In patients receiving late colloids, it may be speculated, that either, the indication is questionable or later instability requiring repeated resuscitation (e.g., bleeding) occurred, both of which will be associated with adverse outcomes.

Second, the use of the first TISS score as a measure of severity of illness neglects the patients' development during ICU stay. Patients with worsening condition might have been severely ill but taken into the analysis as relatively healthy.

Because RaFTA uses data from clinical routine, another source of bias might be incomplete reporting. To analyze this possible source of bias, we did a best/worst-case analysis for 90-day mortality that suggested that any bias introduced by incomplete follow-up would be small.

Conclusion

RaFTA suggests that timing of fluid therapy with colloids in ICU patients might influence the outcome in day-to-day clinical routine. This might be due to the non-indicated use of colloids or the failure of resuscitation.

Clinical Significance

Early resuscitation of critically ill patients with colloids showed no negative effects in the present analysis. Elucidating the actual benefits of early colloids remains an open question for future research.

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Table 4: Odds ratios for RIFLE failure in the total study population and national subgroups

	Total (n = 2,621)			*India (n = 1,933)*		
Effects	*Sig.*	*OR*	*95% CI*	*Sig.*	*OR*	*95% CI*
Gender (M vs F)	0.014	0.746	0.590 0.943	0.028	0.735	0.559 0.967
Sepsis at admission (y/n)	0.008	1.387	1.091 1.763	0.006	1.469	1.117 1.932
Chronic kidney disease at admission (y/n)	<0.001	10.860	8.549 13.795	<0.001	8.991	6.819 11.854
First therapeutic intervention scoring system	<0.001	1.420	1.256 1.605	<0.001	1.464	1.272 1.685
Cumulative fluid balance	<0.001	1.032	1.018 1.047	0.001	1.026	1.011 1.042
Initial colloid dose (first day with colloids)	0.635	1.094	0.754 1.588	0.626	1.148	0.660 1.997
Vasopressors (y/n)	<0.001	1.981	1.488 2.639	0.002	1.691	1.209 2.365
	Malaysia (n = 312)			*Taiwan (n = 376)*		
Effects	*Sig.*	*OR*	*95% CI*	*Sig.*	*OR*	*95% CI*
Gender (M vs F)	0.138	0.565	0.266 1.200	0.884	1.051	0.539 2.051
Sepsis at admission (y/n)	0.264	1.492	0.740 3.009	0.133	3.230	0.699 14.923
Chronic kidney disease at admission (y/n)	<0.001	37.467	17.588 79.815	<0.001	13.642	5.976 31.142
First therapeutic intervention scoring system	0.213	1.345	0.843 2.146	0.850	1.036	0.717 1.498
Cumulative fluid balance	<0.001	1.128	1.060 1.199	0.126	1.053	0.986 1.125
Initial colloid dose (first day with colloids)	0.343	0.674	0.298 1.525	0.568	1.323	0.507 3.455
Vasopressors (y/n)	0.121	1.914	0.843 4.345	<0.001	14.101	4.539 43.803

y, yes; n, no; M, male; F, female

Table 5: Odds ratios for the use of renal replacement therapy in the total study population and national subgroups

	Total (n = 2,321)			*India (n = 1,933)*		
Effects	*Sig.*	*OR*	*95% CI*	*Sig.*	*OR*	*95% CI*
Gender (M vs F)	0.978	1.004	0.750 1.344	0.912	1.020	0.718 1.449
Sepsis at admission (y/n)	0.012	1.454	1.087 1.945	0.004	1.653	1.169 2.337
Chronic kidney disease at admission (y/n)	<0.001	8.058	6.025 10.777	<0.001	6.047	4.263 8.578
First therapeutic intervention scoring system	<0.001	1.647	1.404 1.932	<0.001	1.722	1.426 2.080
Cumulative fluid balance	0.068	0.977	0.953 1.002	0.092	0.974	0.944 1.004
Initial colloid dose (first day with colloids)	0.392	1.200	0.791 1.821	0.808	0.918	0.460 1.832
Vasopressors (y/n)	<0.001	2.649	1.949 3.600	<0.001	2.345	1.619 3.398
	Malaysia (n = 312)			*Taiwan (n = 376)*		
Effects	*Sig.*	*OR*	*95% CI*	*Sig.*	*OR*	*95% CI*
Gender (M vs F)	0.305	0.686	0.334 1.409	0.214	1.855	0.700 4.916
Sepsis at admission (y/n)	0.601	1.204	0.600 2.415	0.999	0.000	0.000
Chronic kidney disease at admission (y/n)	<0.001	19.581	9.415 40.720	<0.001	13.225	4.922 35.532
First therapeutic intervention scoring system	0.084	1.524	0.945 2.457	0.288	1.359	0.772 2.392
Cumulative fluid balance	0.624	1.014	0.959 1.073	0.627	0.977	0.887 1.075
Initial colloid dose (first day with colloids)	0.821	0.919	0.439 1.920	0.229	2.050	0.637 6.601
Vasopressors (y/n)	0.009	2.806	1.298 6.069	<0.001	7.841	2.685 22.898

y, yes; n, no; M, male; F, female

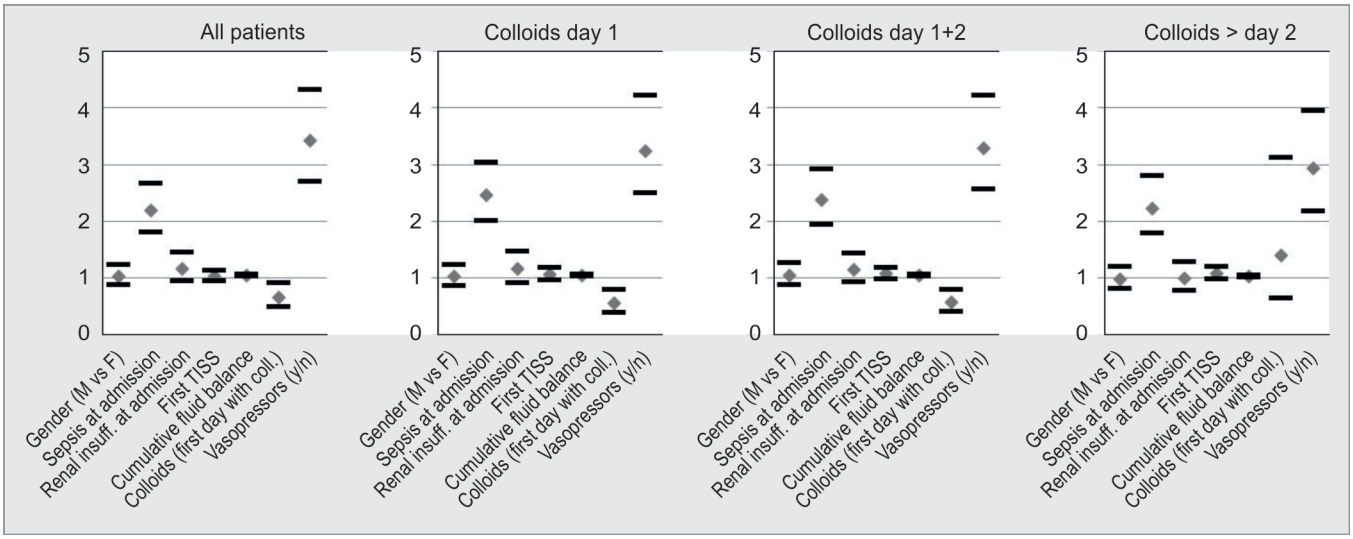

Fig. 3: Odds ratios of a logistic regression model for 90-day mortality in all patients. The number of patients for these subgroups is 2,471; 2,157; 2,282; 1,828. All subgroups include patients receiving no colloids or those receiving colloids on the indicated day(s). TISS, therapeutic intervention scoring system

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Ethics Approval and Consent to Participate

The protocol was approved by the ethics committees of the Ärztekammer Westfalen-Lippe as an extension of the previous RaFTinG registry (2009-366-f-S). Written informed consent was obtained to allow follow-up after 90 days. For patients who did not reach the ability to decide on their consent and had no representative, no follow-up was performed.

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