Original Article

Fluid resuscitation of at least 30 mL/kg was not associated with decreased mortality in patients with infection, signs of hypoperfusion, and a do-not-intubate order

Wataru Matsuda, Yumi Funato, Momoyo Miyazaki, and Koichiro Tomiyama

Department of Emergency Medicine and Critical Care, Center Hospital of the National Center for Global Health and Medicine, Toyama, Shinjuku, Tokyo, Japan

Aim: Administration of at least 30 mL/kg of fluid as fluid resuscitation is recommended for patients with sepsis and signs of hypoperfusion. However, it is not clear whether this is appropriate for patients with a do-not-intubate (DNI) order. This study evaluated the association between volume of fluid resuscitation and outcomes in patients with infection, signs of hypoperfusion, and a DNI order in an emergency department.

Methods: This was a single-center retrospective cohort study. We classified the infected patients with signs of hypoperfusion and a DNI order seen in our emergency department between April 1, 2015 and November 31, 2020 into the standard fluid resuscitation group (≥30 mL/kg) and the restricted fluid resuscitation group (<30 mL/kg). We compared with in-hospital mortality and the rate of discharge to home in two groups.

Results: Of 367 patients, 149 received standard fluid resuscitation and 218 received restricted fluid resuscitation. In-hospital mortality was similar in each group (40/149 and 62/218, respectively). Standard fluid resuscitation was not associated with in-hospital mortality (adjusted odds ratio [aOR], 1.05; 95% confidence interval [CI], 0.62–1.77, P = 0.86), but was associated with a significantly lower rate of discharge to home (aOR, 0.55; 95% CI, 0.30–0.98, P = 0.043). There was no significant difference in respiratory rate or need for oxygen therapy post-resuscitation between the two groups.

Conclusion: This study suggests that fluid resuscitation may be not beneficial for infected patients with signs of hypoperfusion and a DNI order. Further studies should be conducted on the options for resuscitation management for these patients.

Key words: Do-not-intubate order, fluid resuscitation, respiratory insufficiency, sepsis, shock

INTRODUCTION

SEPSIS IS A life-threatening disease and often requires long-term mechanical ventilation. However, some patients with infection and suspected sepsis who present to the emergency department have a do-not-intubate (DNI) order in place. Although the rate of DNI orders among these patients is not known, it is reported that 14–38% of patients with acute respiratory failure, who often overlap with sepsis, have such orders in place and that the number of DNI orders is increasing worldwide.[1] It is known that patients with DNI orders tend not to receive other invasive treatments,[2] however, they do not reject all intensive care options for lifesaving. Therefore, we believe that it is important to investigate appropriate management of these patients in the emergency department.

For sepsis accompanied by hypotension or hyperlactatemia, the international guideline recommends administration of at least 30 mL/kg of fluid as fluid resuscitation.[3,4] Despite the low quality of evidence for this recommendation, fluid resuscitation is one of the major treatments for sepsis. In some areas, such as New York, compliance with a treatment protocol that includes fluid resuscitation is required by law.[5]

A recent systematic review of 17 observational studies reported that protocols, which included high-volume fluid resuscitation were associated with increased survival.[6] However, these studies did not focus on patients with a DNI order. Because fluid overload can be harmful to the patient, the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (J-

Corresponding: Wataru Matsuda, MD, Department of Emergency Medicine and Critical Care, Center Hospital of the National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku, Tokyo 162-8655, Japan. E-mail: wmatsuda@hosp.ncgm.go.jp.

Received 18 May, 2022; accepted 12 Sep, 2022

Funding Information

No funding information provided.

SSCG2020) recommend that the physician carefully observe the patient to avoid excessive fluid loads.[7] Fluid overload because of resuscitation may lead to exacerbation of respiratory failure, which might not be overcome without mechanical ventilation. This would prove fatal for patients with a DNI order.

This study aimed to evaluate the association between administering the internationally recommended ≥30 mL/kg of fluid for fluid resuscitation and outcomes in patients with infection, signs of hypoperfusion, and a DNI order.

METHODS

Ethical approval and informed consent

THE STUDY WAS approved by the ethics committee of our hospital (approval number: NCGM-S-004282-00). Informed consent was obtained using the opt-out method *via* the hospital website.

Study design and setting

The setting of this single-center retrospective cohort study was the emergency department of an urban tertiary care hospital in Japan. Our emergency department had no mandatory protocol for fluid administration to infected patients with signs of hypoperfusion and a DNI order. Therefore, fluids for fluid resuscitation could be restricted to below 30 mL/kg at the discretion of the attending physician.

Most of the patients arrived by ambulance, and it rarely took more than 1 h to start fluid infusion after triage. We used balanced crystalloids for resuscitation to prevent metabolic acidosis because of high-volume fluid unless hyperkalemia was present.[8] In accordance with international clinical practice guidelines,[3] the attending physician usually administered fluid resuscitation of at least 30 mL/kg to infected patients with signs of hypoperfusion. In addition, they used point-of-care ultrasound as needed to evaluate the responsiveness and tolerability of fluid resuscitation. However, there were no treatment protocols for patients with a DNI order, and it was possible to restrict fluid resuscitation at the discretion of the attending physician. Patients stayed in the emergency department until standard or restricted fluid resuscitation was completed. Fluid resuscitation was not given after admission unless the patient's condition worsened.

Inclusion and exclusion criteria

Patients with infection, signs of hypoperfusion, and a DNI order who received fluid infusion in our emergency department were included in the study. Because it was not described in the medical records whether a DNI order was present prior to triage, we judged eligibility based on whether there was a record of receiving a DNI order within 24 h after triage. We defined signs of hypoperfusion as impaired tissue perfusion indicated by systolic blood pressure ≤100 mm Hg or a lactate level ≥4.0 mmol/L. An international guideline recommends fluid resuscitation for patients with sepsis and hypotension or a lactate level ≥4.0 mmol/L.[4] Specific thresholds for hypotension have not been defined, but systolic blood pressure ≤100 mm Hg is part of the quick Sequential Organ Failure Assessment (qSOFA) and has been proposed as a sign that should raise suspicion for sepsis. Therefore, we considered a systolic blood pressure ≤100 mm Hg to be an indication for fluid resuscitation.[9] The exclusion criteria were (i) fluid overload based on echocardiography according to point-of-care ultrasound and (ii) missing data for the amount of fluid volume administered in the emergency department.

Patients were classified into two groups according to the volume of fluid administered for fluid resuscitation in the emergency department: standard group (≥30 mL/kg) and restricted group (<30 mL/kg).

Collection of data

Information was collected on age, sex, weight, whether or not the patient was admitted from a nursing home, past medical history, clinical frailty scale, vital signs at triage (systolic blood pressure, Glasgow Coma Scale, respiratory rate), serum lactate level, fluid volume administered in the emergency department, and whether or not respiratory support or a vasopressor was used.

The primary endpoint was in-hospital mortality. The secondary outcomes were discharge to home, death within day 7 or 14, tachypnea on days 1 and 4, and need for oxygen therapy on day 4. We used the worst values to evaluate the respiratory rate and fraction of inspired oxygen of oxygen therapy administered if repeated measurements were obtained. Respiratory support was categorized as use of a conventional oxygen device (i.e., a standard nasal cannula, non-rebreather facemask, reservoir mask, or Venturi mask), high-flow nasal cannula (HFNC), or non-invasive ventilation (NIV). Frailty was defined as a Clinical Frailty Scale score >4.[10]

Statistical analysis

We used Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. In-hospital mortality was analyzed using Kaplan–Meier curves and the log-rank test. Age, sex, whether or not the admission was from a nursing home, severe comorbidities, lower respiratory tract infection,

qSOFA score, and hyperlactatemia were used as covariates in the logistic regression analysis. In addition, we also performed sensitivity analysis with different covariates. The qSOFA score and serum lactate level measured in the emergency department have been shown to affect the prognosis in patients with infection and are used as an adjunct to the diagnosis of sepsis in the Sepsis-3 definition.[9] We defined severe comorbidity as chronic heart, respiratory, kidney, or liver disease.[11] Statistical significance was set to P value <0.05 and power was set to 80%. Data such as body weight and serum lactate levels were not expected to be available for some patients. Because these data were not completely at random, exclusion could affect the results. We, therefore, imputed the missing data with predicted data calculated by linear regression models with the advice of statisticians.

Age, sex, clinical frailty scale, past medical history, and admission from a nursing home were used to calculate body weight. Age, sex, clinical frailty scale, admission from a nursing home, initial vital signs, lower respiratory infection, diagnosis of sepsis, fluid volume, respiratory support, and vasopressor use were used to calculate serum lactate level. Statistical analysis was performed using R version 3.4.1.

RESULTS

WE REVIEWED THE cases of 367 eligible patients in the study period, 149 of whom received a fluid volume of ≥30 mL/kg (Fig. 1). Table 1 shows patient demographics and clinical characteristics. Most patients were underweight and frail. Patients who were male, had low body weight, had lower respiratory tract infection, or were in a more severe condition, tended to receive fluid resuscitation of ≥30 mL/kg. The median volume of fluid administered in the emergency department was 48.1 mL/kg in the standard group and 15.2 mL/kg in the restricted group. Vasopressor use was more frequent in the standard group, but was administered only in a small number of cases. Data on weight were missing in 49 patients (13%) and on the serum lactate level in 45 patients (12%).

The in-hospital mortality was similar in both groups (Table 2, Fig. 2). In addition, the respiratory rate on both day 1 and day 4 was not significantly different between the two groups. The fraction of inspired oxygen required on day 4 was also similar between the groups. Moreover, the rate of discharge to home was significantly lower in the standard group (Table 2, Fig. 3).

Table 3 showed the outcomes of multivariable analysis. Standard fluid resuscitation was not significantly associated with in-hospital mortality (adjusted OR [aOR], 1.05; 95% confidence interval [CI], 0.62–1.77, P = 0.86), but was associated with a significantly lower rate of discharge to home (aOR, 0.55, 95% CI, 0.30–0.98, P = 0.043). Some sensitivity analyzes showed similar results to the original analysis (Tables S1–S3).

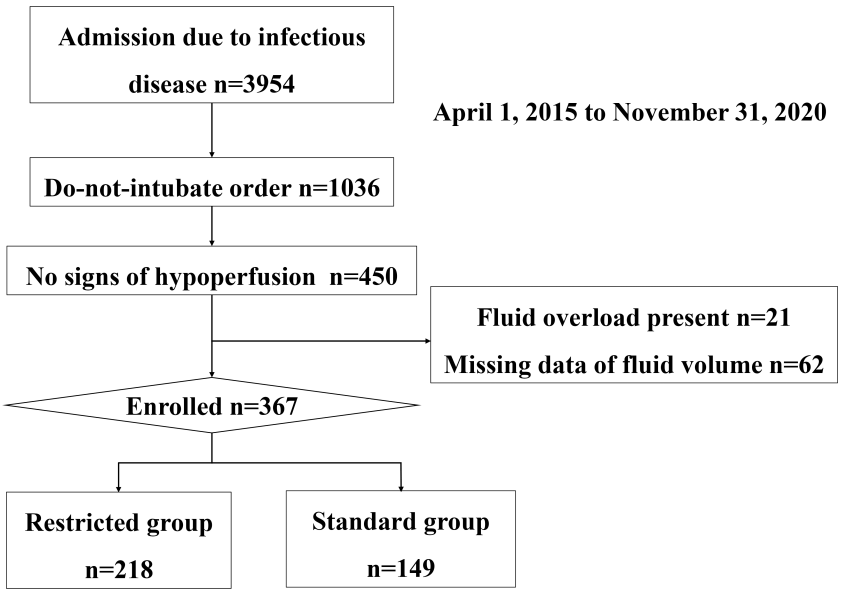

Fig. 1. Flow of participants in this study. *Presence/absence of fluid overload present was evaluated by an emergency physician using point-of-care ultrasound.

Table 1. Patient demographics and clinical characteristics

Variable	Restricted group (*n* = 218)	Standard group (*n* = 149)	*P*-value*
Age, years, median [25%, 75%]	87 [83, 92]	87 [82, 92]	0.99
Male, *n* (%)	121 (56)	62 (42)	0.011
Body mass index, median [25%, 75%]	18.6 [16.3, 21.8]	17.9 [15.6, 19.8]	0.020
Weight, kg, median [25%, 75%]	45 [38, 53]	40 [35, 46]	<0.001
Missing data, *n* (%)	26 (12)	23 (15)	
Weight after imputation, kg, median [25%, 75%]	45 [38, 52]	40 [37, 47]	<0.001
Admission from a nursing home, *n* (%)	81 (37)	59 (40)	0.66
Frailty			
Not frail (CFS 1–3), *n* (%)	16 (7)	10 (7)	0.21
Pre-frail (CFS 4), *n* (%)	27 (12)	10 (7)	
Frail (CFS 5–9), *n* (%)	175 (80)	129 (87)	
Past medical history			
Chronic respiratory disease, *n* (%)	42 (19)	17 (11)	0.06
Chronic cardiovascular disease, *n* (%)	79 (36)	44 (30)	0.22
Chronic kidney disease, *n* (%)	23 (11)	6 (4)	0.029
Chronic liver disease, *n* (%)	7 (3)	4 (3)	>0.99
Hypertension, *n* (%)	71 (33)	52 (35)	0.65
Malignant disease, *n* (%)	49 (22)	37 (25)	0.62
Any severe comorbidity, *n* (%)	119 (55)	61 (41)	0.011
Source of infection, *n* (%)			
Respiratory, *n* (%)	174 (80)	83 (56)	<0.001
Urinary, *n* (%)	27 (12)	37 (25)	
Abdominal, *n* (%)	6 (3)	20 (13)	
Others, *n* (%)	11 (5)	9 (6)	
qSOFA positive, *n* (%)	135 (62)	111 (74)	0.013
Respiratory rate, median [25%, 75%]	24 [19, 28]	24 [18, 27]	0.27
Systemic blood pressure, mm Hg, median [25%, 75%]	113 [98, 133]	97 [81, 118]	<0.001
Glasgow Coma Scale, median [25%, 75%]	13 [10, 14]	12 [10, 14]	0.007
Sepsis, *n* (%)	199 (91)	139 (93)	0.56
Serum lactate, mmol/L, median [25%, 75%]	2.1 [1.3, 3.8]	2.9 [1.9, 4.4]	<0.001
Missing data, *n* (%)	30 (14)	15 (10)	
Serum lactate ≥4.0 mmol/L, *n* (%)	45 (23)	46 (34)	0.045
Serum lactate after imputation, mmol/L, median [25%, 75%]	2.1 [1.3, 3.6]	3.0 [2.1, 4.3]	<0.001
Serum lactate ≥4.0 mmol/L after imputation, *n* (%)	48 (22)	50 (34)	0.016
Treatment in ED			
Vasopressor, *n* (%)	7 (3)	16 (11)	0.004
Respiratory support, *n* (%)			0.06
Conventional oxygen therapy, *n* (%)	147 (67)	111 (74)	
High-flow nasal cannula, *n* (%)	17 (8)	14 (9)	
Non-invasive ventilation, *n* (%)	11 (5)	1 (1)	
Fluid volume, mL, median [25%, 75%]	650 [500, 1,000]	2,100 [1,500, 2,800]	<0.001
Fluid volume, mL/kg, median [25%, 75%]	15.2 [10.8, 22.1]	48.1 [37.3, 71.2]	<0.001
Time in ED, min, median [25%, 75%]	273 [210, 349]	320 [252, 412]	<0.001

CFS, clinical frailty scale; ED, emergency department; qSOFA, quick Sequential Organ Failure Assessment.
*Categorical variables were analyzed by Fisher's exact test and continuous variables by the Mann–Whitney *U* test.

Table 2. Primary and secondary outcomes

Outcome	Restricted (n = 218)	Standard (n = 149)	P-value*
Primary outcome			
In-hospital death, n (%)	62 (28)	40 (27)	0.81
Secondary outcomes			
Discharge to home, n (%)	67 (31)	29 (19)	0.016
Death within 14 days, n (%)	37 (17)	31 (21)	0.41
Respiratory rate on day 1, n (%)	24 [20, 30]	25 [21, 30]	0.81
Respiratory rate on day 4, n (%)	20 [18, 25]	21 [18, 25]	0.37
Need for respiratory support on day 4, n (%)			
No need	100 (46)	66 (44)	0.61
FiO_2 < 0.4	67 (31)	47 (32)	
FiO_2 0.4–0.6	19 (9)	7 (5)	
FiO_2 ≥ 0.6	9 (4)	5 (3)	

FiO_2, fraction of inspired oxygen.
*Categorical variables were analyzed by Fisher's exact test and continuous variables by the Mann–Whitney U test.

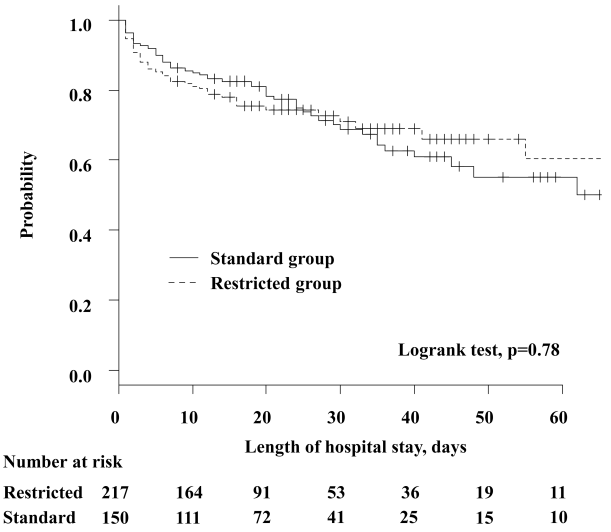

Fig. 2. Kaplan–Meier curves for the standard and restricted fluid resuscitation groups.

DISCUSSION

IN THIS STUDY, only 41% of infected patients with signs of hypoperfusion and a DNI order received administration of ≥30 mL/kg of fluid in our emergency department. Although the administration rate of this internationally

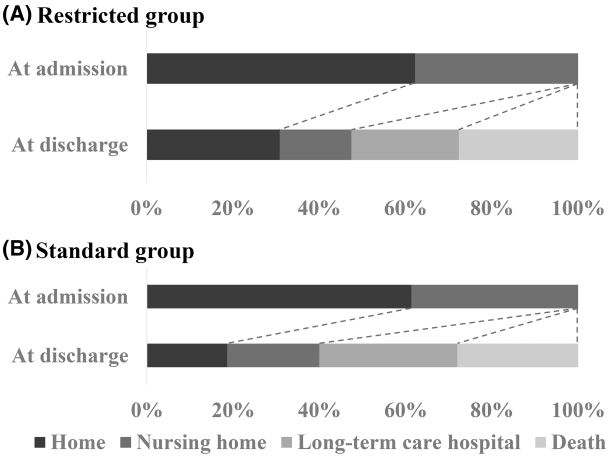

Fig. 3. Discharge destination in the standard and restricted fluid resuscitation groups.

recommended volume for fluid resuscitation was low in this specific population, no association was seen with in-hospital mortality after controlling for various confounders. In addition, both the standard and restricted fluid resuscitation groups had similar respiratory rate on days 1 and 4 and similar need for oxygen therapy post-resuscitation. However, the standard group had a significantly lower rate of discharge to home although respiratory status was not significantly different between the two groups.

We have some ideas that may explain the reasons for these results. First, this result is similar to the results of a previous study in high-risk patients. Truong *et al.*[11] reported no association between fluid resuscitation and mortality even when compliance with internationally recommended volume for fluid resuscitation was low in septic patients with heart failure, end-stage renal disease, or cirrhosis. Because many of patients had any comorbidities, the high-dose fluid may have been harmful to them. In addition, most of the patients in this study were also frail. Because frailty has been reported to be associated with mortality and the need for organ support,[12] we considered that patients with frailty might have a poor response to fluid resuscitation. Second, the rate of vasopressor use was low in our study although the current international guideline recommends early use of vasopressor.[4] It has been reported that patients with a DNI order tend not to receive other kinds of intensive care.[2] Similarly, in our hospital, some patients might not have received vasopressors despite their medical indications because of the DNI. As early use of vasopressor may prevent fluid overload,[13] our results might have been different if we had ensured early use of vasopressors.

There was no difference in respiratory status after resuscitation between the two groups. Some studies have also

Table 3. Results of multivariable analysis

	In-hospital mortality		Discharge to home	
Variables	OR (95% CI)	*P* value*	OR (95% CI)	*P* value*
Fluid ≥30 mL/kg	1.15 (0.69–1.92)	0.60	0.50 (0.28–0.89)	0.018**
Age	1.00 (0.98–1.03)	0.74	0.98 (0.95–1.01)	0.16
Male	1.13 (0.67–1.89)	0.65	0.88 (0.50–1.56)	0.67
Admission from a nursing home	0.84 (0.49–1.42)	0.51	0.08 (0.04–0.19)	<0.001**
Severe comorbidities	1.95 (1.19–3.19)	0.008**	1.02 (0.60–1.74)	0.94**
Lower respiratory infection	2.90 (1.56–5.41)	<0.001**	0.61 (0.34–1.10)	0.10
qSOFA positive	1.43 (0.83–2.47)	0.20	0.72 (0.42–1.24)	0.24
Serum lactate ≥4 mmol/L	2.14 (1.25–3.64)	0.005**	0.42 (0.22–0.82)	0.010**

OR, odds ratio; qSOFA, quick Sequential Organ Failure Assessment.
*Logistic regression analysis was used to analyze.
**Indicates a significant difference.

reported that fluid administration of around 30 mL/kg was not associated with intubation rate.[14,15] Given that the median infusion volume in our standard group was not very high at 45 mL kg, we considered that the risk of severe respiratory failure with fluid resuscitation might be low. In addition, because these patients could receive noninvasive positive pressure ventilation or HFNC as needed, they might have survived even if their respiratory failure worsened.[16,17]

Because of the retrospective nature of this study, the severity of shock was adjusted only by systolic blood pressure at triage and an initial serum lactate level. If the response to bolus fluid administration was poor, more fluid might have been administered. Therefore, this study cannot conclude that restriction of fluid resuscitation is appropriate. However, in a previous study,[14] fluid resuscitation consistently tended to reduce mortality in a subgroup of patients at various high risks, whereas this study failed to show benefits.

Although initial resuscitation and hemodynamic managements in infected patients with a DNI order has not previously received much attention, they may respond differently to treatment than the known patient population. We believe that further research is desirable to improve the quality of care for patients with a DNI order.

This study has several limitations. First, we could not collect the time taken for >30 mL/kg of fluid resuscitation. Post-resuscitation fluid volume, such as within 24 h of admission, might have affected outcomes. In addition, although previous studies have suggested it is preferable to administer >30 mL/kg of fluid within 3 h[14,18] the volume of fluid administered within this time frame was unclear in the present study. However, the median length of stay in the emergency department was well above 3 h, and we think that most patients in the restricted group received <30 mL/kg of fluid within 3 h. Second, some patients did not meet the criteria for sepsis. However, because the diagnosis requires waiting for fluid response and blood tests, fluid resuscitation should be started when sepsis is suspected. Therefore, we included infected patients with hypotension or hyperlactatemia, regardless of a confirmed diagnosis of sepsis. Third, the lactate clearance could not be considered in the analysis, although it might have affected the amount of fluid infusion. Finally, most of the patients in this study had very low body mass index. Although Japanese tend to be thin, there were many underweight patients in this study. Additionally, patients with a DNI order are prone to emaciation in very old age or have comorbidities, so this could also have been a contributing factor. Given that obese patients have been reported to have better outcomes[19] and tend to receive lower fluid volumes per body weight,[13] further investigations are needed to confirm whether the results of this study are similar for patients who are not considered underweight.

CONCLUSIONS

THIS STUDY SUGGESTS that fluid resuscitation may be not beneficial for infected patients with signs of hypoperfusion and a DNI order. Further studies are warranted to examine options for resuscitation management in such patients.

DISCLOSURE

APPROVAL OF THE Research Protocol: This study was approved by the Ethics Committee of the Center Hospital of the National Center for Global Health and Medicine (Approval Number: NCGM-S-004282-00).

Informed Consent: Based on the opt-out approach, we disclosed information about this study and excluded data when the patient declined to participate directly or *via* proxy.

Registry and the Registration No. of the Study: N/A.

Animal Studies: N/A.

Conflict of Interest: None declared.

ACKNOWLEDGEMENTS

THE AUTHORS THANK Yukari Uemura (Biostatistics Section, Department of Data Science, Center for Clinical Science, and National Center for Global Health and Medicine, Tokyo, Japan) for advice on statistical analysis.

REFERENCES

1 Wilson ME, Mittal A, Karki B *et al*. Do-not-intubate orders in patients with acute respiratory failure: a systematic review and meta-analysis. Intensive Care Med. 2020; 46: 36–45.
2 Sarkari NN, Perman SM, Ginde AA. Impact of early do-not-attempt-resuscitation orders on procedures and outcomes of severe sepsis. J. Crit. Care 2016; 36: 134–9.
3 Evans L, Rhodes A, Alhazzani W *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and Septic Shock 2021. Crit. Care Med. 2021; 49: e1063–e143.
4 Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Crit. Care Med. 2018; 46: 997–1000.
5 Seymour CW, Gesten F, Prescott HC *et al*. Time to treatment and mortality during mandated emergency care for sepsis. N. Engl. J. Med. 2017; 376: 2235–44.
6 Pepper DJ, Sun J, Cui X, Welsh J, Natanson C, Eichacker PQ. Antibiotic- and fluid-focused bundles potentially improve sepsis management, but high-quality evidence is lacking for the specificity required in the centers for medicare and medicaid service's sepsis bundle (SEP-1). Crit. Care Med. 2019; 47: 1290–300.
7 Egi M, Ogura H, Yatabe T *et al*. The Japanese clinical practice guidelines for management of sepsis and septic shock 2020 (J-SSCG 2020). J. Intensive Care 2021; 9: 53.
8 Semler MW, Self WH, Wanderer JP *et al*. Balanced crystalloids versus saline in critically ill adults. N. Engl. J. Med. 2018; 378: 829–39.
9 Singer M, Deutschman CS, Seymour CW *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315: 801–10.
10 Fernando SM, McIsaac DI, Perry JJ *et al*. Frailty and associated outcomes and resource utilization among older ICU patients with suspected infection. Crit. Care Med. 2019; 47: e669–e76.
11 Truong TN, Dunn AS, McCardle K *et al*. Adherence to fluid resuscitation guidelines and outcomes in patients with septic shock: reassessing the "one-size-fits-all" approach. J. Crit. Care 2019; 51: 94–8.
12 Zampieri FG, Iwashyna TJ, Viglianti EM *et al*. Association of frailty with short-term outcomes, organ support and resource use in critically ill patients. Intensive Care Med. 2018; 44: 1512–20.
13 Macdonald SPJ, Keijzers G, Taylor DM *et al*. Restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH): a pilot randomised controlled trial. Intensive Care Med. 2018; 44: 2070–8.
14 Kuttab HI, Lykins JD, Hughes MD *et al*. Evaluation and predictors of fluid resuscitation in patients with severe sepsis and septic shock. Crit. Care Med. 2019; 47: 1582–90.
15 Khan RA, Khan NA, Bauer SR *et al*. Association between volume of fluid resuscitation and intubation in high-risk patients with sepsis, heart failure, end-stage renal disease, and cirrhosis. Chest 2020; 157: 286–92.
16 Wilson ME, Majzoub AM, Dobler CC *et al*. Noninvasive ventilation in patients with do-not-intubate and comfort-measures-only orders: a systematic review and meta-analysis. Crit. Care Med. 2018; 46: 1209–16.
17 Wilson ME, Mittal A, Dobler CC *et al*. High-flow nasal cannula oxygen in patients with acute respiratory failure and do-not-intubate or do-not-resuscitate orders: a systematic review. J. Hosp. Med. 2020; 15: 101–6.
18 Tigabu BM, Davari M, Kebriaeezadeh A, Mojtahedzadeh M. Fluid volume, fluid balance and patient outcome in severe sepsis and septic shock: a systematic review. J. Crit. Care 2018; 48: 153–9.
19 Pepper DJ, Sun J, Welsh J, Cui X, Suffredini AF, Eichacker PQ. Increased body mass index and adjusted mortality in ICU patients with sepsis or septic shock: a systematic review and meta-analysis. Crit. Care 2016; 20: 181.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Results of sensitivity analysis (A).
Table S2 Results of sensitivity analysis (B).
Table S3 Results of sensitivity analysis (C).