ICU-free days as a more sensitive primary outcome for clinical trials in critically ill pediatric patients

Hanjin Cho MD, PhD1 | Barbara Wendelberger PhD2 | Marianne Gausche-Hill MD3,4,5,6 | Henry E Wang MD, MS7 | Matthew Hansen MD, MCR8 | Nichole Bosson MD, MPH3,4,6 | Roger J. Lewis MD, PhD2,4,6

1 Department of Emergency Medicine, College of Medicine, Korea University, Seoul, Korea
2 Berry Consultants, LLC, Austin, Texas, USA
3 Los Angeles County Emergency Medical Services Agency, Santa Fe Springs, California, USA
4 Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California, USA
5 Departments of Pediatrics, Harbor-UCLA Medical Center, Torrance, California, USA
6 Department of Emergency Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, USA
7 Department of Emergency Medicine, The Ohio State University, Columbus, Ohio, USA
8 Department of Emergency Medicine, Oregon Health and Science University, Portland, Oregon, USA

Correspondence
Roger J. Lewis, MD, PhD, Department of Emergency Medicine, Harbor-UCLA Medical Center, 1000 West Carson Street, Box 21, Torrance, CA 90509 USA.
Email: roger@emedharbor.edu

Funding and support: By JACEP Open policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

See Editorial: https://doi.org/10.1002/emp2.12496

Abstract

Background: Our objective was to assess the association between intensive care unit (ICU)-free days and patient outcomes in pediatric prehospital care and to evaluate whether ICU-free days is a more sensitive outcome measure for emergency medical services research in this population.

Methods: This study used data from a previous pediatric prehospital trial. The original study enrolled patients ≤12 years of age and compared bag-valve-mask-ventilation (BVM) versus endotracheal intubation (ETI) during prehospital resuscitation. For the current study, we defined ICU-free days as 30 minus the number of days in the ICU (range, 0–30 days) and assigned 0 ICU-free days for death within 30 days. We compared ICU-free days between the original study treatment groups (BVM vs ETI) and with the original trial outcomes of survival to hospital discharge and Pediatric Cerebral Performance Category (PCPC).

Results: Median ICU-free days for the BVM group (n = 404) versus ETI group (n = 416) was not statistically different: 0 ICU-free days (interquartile range, 0–10) versus 0 (0–0), P = 0.219. Median ICU-free days were greater for BVM group in 3 subgroups: foreign body aspiration 30 (0–30) versus 0 (0–21), P = 0.028; child maltreatment 0 (0–14.2) versus 0 (0–0), P = 0.004; and respiratory arrest 25 (1–29) versus 7.5 (0–27.7), P = 0.015. In the original trial, neither survival nor PCPC demonstrated differences in all 3 subgroups—survival was greater with BVM for child maltreatment and respiratory arrest and favorable PCPC was greater with BVM for foreign body aspiration. Overall, in the current study, patients with more ICU-free days also had greater survival to hospital discharge and more favorable PCPC scores.

Conclusions: This initial study of the association between ICU-free days and patient outcomes during prehospital pediatric resuscitation appears to support the use of ICU-free days as a clinical endpoint in this population. ICU-free days may be more sensitive than either mortality or PCPC alone while capturing aspects of both measures.
INTRODUCTION

1.1 Background

The design of a clinical trial in critically ill or injured pediatric patients, a highly heterogeneous population, ideally centers on a patient-centered primary outcome, one that captures both the desirability of each patient’s clinical course and their final status. This population may be affected by serious illness with extremely high mortality (eg, sudden infant death syndrome and cardiac arrest), high morbidity but low mortality (eg, severe asthma exacerbations), or both high mortality and morbidity (eg, multiple traumatic injuries).1,2 Thus, a generally applicable outcome measure must capture both mortality and the speed or extent of recovery, the latter reflecting the degree of morbidity associated with the acute illness or injury.2–6

Traditionally, outcome measures in cardiac arrest resuscitation research have focused on processes of care (eg, response times and procedure success) and clinical outcomes (eg, return of spontaneous circulation, survival and neurological outcome).1,7–10 The traditional clinical outcomes are usually binary variables. A common challenge to the design of resuscitation trials is that the reliance on traditional binary outcome can result in large minimum sample sizes, which make the trial logistically challenging or impossible. Even more problematic is applying precious and extensive resources to conduct a clinical trial in which important differences in clinical outcomes are not detected because the main outcome measure lacked sensitivity for the true differences. Investigators have explored alternative outcome measures, such as the length of time a patient requires care in an intensive care unit (ICU) (eg, ICU days or days on mechanical ventilation).11–14 However, a shorter ICU stay may result from either a rapid recovery or an early death.15–20

A common solution to the problems with traditional outcome measures is to use treatment-free days (eg, ICU-free days and ventilator-free days), defined as the length of time, within a pre-specified period, for which the patient is alive and free of the specific treatment being tracked.21–23 A number of authors have suggested using ICU-free days as a standard main outcome measure for clinical trials. ICU-free days assumes that remaining in the ICU is a general indicator of the ongoing severity of illness, with the additional caveat that any patient who dies within the period of observation (eg, 30 or 90 days) is assigned zero ICU-free days, even if they were transferred out of the ICU and alive for some period during their hospital stay.22,23

1.2 Importance

Emergency medical services (EMS) research will benefit from a generally applicable outcome measure that captures both the final mortality outcome and the speed of recovery. Moreover, such an outcome measure would likely be a more sensitive measure of treatment effect than mortality or other binary outcomes. A more sensitive main outcome measure, as the basis for a trials sample size calculation, might also lead to briefer, less expensive research, a critical issue in EMS research. Whether the number of ICU-free days reasonably captures the outcomes of critically ill and injured children, however, is unknown.

1.3 Objective of this study

Our objective was to compare ICU-free days, as an alternative clinical trial outcome, with survival and Pediatric Cerebral Performance Category (PCPC).2,8,9 We used data collected from the Pediatric Airway Management Project—a randomized controlled trial of bag-valve-mask ventilation (BVM) versus endotracheal intubation (ETI) during prehospital airway management in children. In the current study, we compare ICU-free days to the traditional outcomes of survival and neurological outcomes, both for the main treatment groups (BVM vs ETI) and patient subgroups.

METHODS

2.1 Study design

This study is a secondary analysis of data collected prospectively during a previous randomized clinical trial.2 We studied an alternative main outcome measure (ICU-free days), which could be derived from the existing clinical trial data.23 This secondary analysis of de-identified data was determined to be exempt from the requirement for Institutional Review Board (IRB) approval.

2.2 Selection of participants and setting

Original study enrollment was conducted from March 15, 1994 to January 1, 1997. Patients were eligible if they were either aged 12 years or younger or estimated to weigh 40 kg or less and if they required airway management based on 1 or more of the following criteria: cardiopulmonary arrest (patient apnea without a palpable pulse); respiratory arrest (patient apnea only, with pulse present); respiratory failure (with respiratory rate >60/min or <12/min) with a non-purposeful response or no response to pain; complete or severe partial airway obstruction; traumatic cardiopulmonary arrest; traumatic respiratory arrest; closed or open head trauma with a non-purposeful response or no response...
to pain; and paramedic assessment that assisted ventilation was necessary.

The original clinical trial was conducted in Los Angeles and Orange Counties, California, which are contiguous metropolitan areas with a well-established EMS system. At the time of the trial, both counties had 2-tiered 911 systems consisting of basic and advanced life support units, and base hospitals provided online medical direction for the out-of-hospital treatment of critically ill pediatric patients. Paramedics transported critically ill or injured pediatric patients according to the appropriate guidelines for each county. Adult ETI and BVM had been practiced in both counties for over 10 years when the study began, though pediatric ETI was introduced specifically for the study.

2.3 | Original study intervention

The design of the trial and the trial results have been published previously. Briefly, paramedics performed airway management for critically ill pediatric patients according to a predetermined protocol. Data were collected by a combination of study form completion (paramedic and ED physician) and structured chart review. Paramedics in the study EMS system received intensive study-specific education on BVM and ETI prior to study commencement. Patients were assigned by calendar day to receive BVM (odd days) or BVM followed by ETI (even days). Pediatric Magill forceps for foreign body removal could be used on either odd or even days when basic life support maneuvers failed.

2.4 | Outcomes

In the original clinical trial, survival to discharge from an acute care hospital and neurological status were evaluated retrospectively, by chart review. Neurological status was classified by a 5-category, ordinal scale based on a modified PCPC: normal or no change from baseline, mild disability, moderate disability, severe disability, or coma or vegetative state.

Relevant patient subgroups were defined prior to the collection of study data based on expert consensus, including experts in pediatric emergency care and EMS. Patient subgroups were based on final diagnosis and included sudden infant death syndrome, submersion injury, head injury, multiple trauma, foreign body aspiration, seizure, child maltreatment, cardiopulmonary arrest, respiratory arrest, and reactive airway disease.

For the current study, ICU data collected in the original trial were used to calculate ICU-free days. We defined the ICU-free days as 30 minus the number of days in the ICU (range, 0–30 days). For patients who survived and were in the ICU for less than 30 days, the ICU-free day’s outcome measure was obtained by subtracting the length of the ICU stay from 30. Any patient who died at any time before or on day 30 was assigned an outcome of zero ICU-free days. Patients in the ICU for 30 or more days were also assigned zero ICU-free days. This approach is reasonable as the neurological status of critically ill patients treated for more than 30 days in the ICU would likely be poor.

3 | RESULTS

3.1 | Enrollment

The original study enrolled 830 patients, with 410 assigned to the BVM group and the remaining 420 to the ETI group. Ten patients were excluded from this analysis due to incomplete records—a 6 in the BVM group and 4 in the ETI group. Data for all the other patients in the population were retained and analyzed according to the intention-to-treat principle. Therefore, the final sample consisted of 820 patients (404 BVM, 416 ETI).

Of the 820 patients analyzed, 587 died (ETI: 306, BVM: 281) and 233 survived (ETI: 110, BVM: 123) during follow-up. The vast majority of deaths occurred early, with 584 (99%) in the first 30 days in the ICU.

3.2 | Patient characteristics

The baseline characteristics of enrolled patients are shown in Table 1 as reported in the original trial. As reported in the original trial publication, median age was 1.2 years for the BVM group and 1 year for the ETI group. We found no statistically significant differences between the treatment groups in gender, ethnicity, emergency department disposition, or subgroups categorized by the apparent etiology of the illness or injury. However, a nominally significant difference was noted in the distribution of patients with a final diagnosis of sudden infant death syndrome.

3.3 | Main outcome

Median ICU-free days was 0 (IQR 0–10) for the 404 patients in the BVM group and 0 (0–0) for the 416 in the ETI group ($P = 0.219$; Table 2).
TABLE 1 Patient demographics by pediatric airway management group

| Demographic characteristic | No. (%) of patients | BVM | ETI | P   |
|----------------------------|--------------------|-----|-----|-----|
| Age (years) median (IQR)   | 1.25 (0.25–3.73)   | 1.0 (0.25–3.33) | 0.77 |
| Sex, male                  | 247/403 (61)       | 236/415 (57) | 0.20 |
| Ethnicity                  |                    |     |     | 0.87 |
| Hispanic                   | 172 (45)           | 174 (44) |     |
| White                      | 106 (28)           | 102 (26) |     |
| Black                      | 69 (18)            | 75 (19) |     |
| Asian                      | 25 (6)             | 26 (7) |     |
| Other                      | 10 (3)             | 15 (4) |     |
| Patient disposition        |                    |     |     | 0.79 |
| Died                       | 219 (54)           | 231 (56) |     |
| ICU                        | 83 (20)            | 77 (18) |     |
| Transfer                   | 67 (17)            | 78 (19) |     |
| Operating room             | 14 (3)             | 16 (4) |     |
| Ward or nursery            | 11 (3)             | 8 (2) |     |
| Home                       | 9 (2)              | 6 (1) |     |
| Patient declared dead      | 123/367 (34)       | 110/369 (30) | 0.28 |
| without resuscitation in   |                    |     |     |     |
| the ED                     |                    |     |     |     |
| Final diagnosis             |                    |     |     |     |
| Sudden infant death syndrome| 59 (14)           | 82 (19) | 0.049|
| Submersion injury           | 56 (14)            | 43 (10) | 0.13 |
| Head injury                 | 27 (7)             | 36 (9) | 0.28 |
| Multiple trauma             | 37 (9)             | 51 (12) | 0.15 |
| Foreign body aspiration     | 13 (3)             | 13 (3) | 0.95 |
| Status epilepticus          | 38 (9)             | 33 (8) | 0.47 |
| Child maltreatment          | 24 (6)             | 22 (5) | 0.70 |
| Cardiopulmonary arrest      | 293 (71)           | 303 (72) | 0.83 |
| Respiratory arrest          | 55 (13)            | 55 (13) | 0.89 |
| Reactive airway disease     | 12 (3)             | 11 (3) | 0.80 |

Abbreviations: BVM, bag-valve-mask ventilation; ETI, endotracheal intubation; IQR, interquartile range; ED, emergency department.

Median ICU-free days was significantly higher for BVM versus ETI in 3 of 10 subgroups: children with foreign body aspiration, child maltreatment, and respiratory arrest (P = 0.028, 0.004, 0.015, respectively).

Figure 1 displays the distributions of ICU-free days, for the overall group and patient subgroups. In the overall and most subgroups, the median ICU-free days is 0; however, for the seizure subgroup, median and interquartile numbers were both greater than 20, showing the highest number of ICU-free days regardless of treatment group. The median values in the foreign body aspiration and respiratory arrest group are also higher than those of the other subgroups.

ICU-free days versus neurological outcomes by treatment group are displayed in Table 3. ICU-free days by neurological outcome across both treatment groups and all patient subgroups are shown in Figure 2.

LIMITATIONS

This study has several important limitations. First, the analyzed dataset is relatively old. Although outcomes for children presenting in cardiac...
### TABLE 2  Subgroup ICU-free days by airway management method

| Final diagnosis                      | BVM (n = 404) Survived to discharge/total patients in group (%)<sup>a</sup> | ICU-free days median (IQR)<sup>b</sup> | ETI (n = 416) Survived to discharge/total patients in group (%)<sup>a</sup> | ICU-free days median (IQR)<sup>b</sup> | P  |
|-------------------------------------|-----------------------------------------------------------------------------|--------------------------------------|-----------------------------------------------------------------------------|--------------------------------------|-----|
| Sudden infant death syndrome        | 0/58 (0)                                                                    | 0 (0–0)                              | 0/80 (0)                                                                    | 0 (0–0)                              | NA  |
| Submersion injury                   | 18/55 (32)                                                                  | 0 (0–10.5)                           | 20/43 (46)                                                                  | 0 (0–28)                             | 0.070 |
| Head injury                         | 8/25 (32)                                                                   | 0 (0–13)                             | 9/36 (25)                                                                   | 0 (0–0)                              | 0.589 |
| Multiple trauma                     | 7/37 (18)                                                                   | 0 (0–0)                              | 12/51 (23)                                                                  | 0 (0–0)                              | 0.326 |
| Foreign body aspiration             | 9/13 (69)                                                                   | 30 (0–30)                            | 5/13 (38)                                                                   | 0 (0–21)                             | 0.028 |
| Seizure                             | 35/37 (94)                                                                  | 29 (27–29)                           | 26/32 (81)                                                                  | 29 (22.2–30)                         | 0.696 |
| Child maltreatment                  | 10/24 (41)                                                                  | 0 (0–14.2)                           | 1/22 (4)                                                                    | 0 (0–0)                              | 0.004 |
| Cardiopulmonary arrest              | 24/290 (8)                                                                  | 0 (0–0)                              | 24/301 (7)                                                                  | 0 (0–0)                              | 0.719 |
| Respiratory arrest                  | 46/54 (85)                                                                  | 25 (1–29)                            | 33/54 (61)                                                                  | 7.5 (0–27.7)                         | 0.015 |
| Reactive airway disease             | 6/12 (50)                                                                   | 14 (0–29)                            | 3/10 (30)                                                                   | 0 (0–16.5)                           | 0.220 |
| Overall                             | 123/404 (30)                                                                | 0 (0–10)                             | 110/416 (26)                                                                | 0 (0–0)                              | 0.219 |

Abbreviations: BVM, bag-valve-mask ventilation; ETI, endotracheal intubation; IQR, interquartile range.

<sup>a</sup>Number of patients in each subgroup based on available data to determine ICU-free days.

<sup>b</sup>Data for ICU days are presented by median and IQR. P calculated by Wilcoxon rank-sum test.

**DISCUSSION**

In this study, we find evidence supporting the use of 30-day ICU-free days as a primary outcome measure for trials that compare therapies for critically ill or injured children in the prehospital setting, using data from the prehospital Pediatric Airway Management Project as the example. The available dataset includes a highly heterogeneous population of critically ill pediatric patients in prospectively defined subgroups with a wide range of outcomes. An ideal measure of clinical trial outcomes captures clinically important and patient-centered values, is objective and simple to implement prospectively or retrospectively, and is at least comparable to traditional outcome measures. When assessing the care of critically ill and injured children, the endpoint of ICU-free days has many of these desirable characteristics, and is a common alternative outcome measure. ICU-free days also captures factors related to the cost of care and the use of hospital resources. The ICU-free days outcome measure may allow for more efficient clinical trial implementation and data collection because it is an outcome that is readily available from administrative and electronic health records. It has broader applicability compared with other, disease-specific outcomes. This is ideal for clinical trials that aim to study interventions, such as prehospital pediatric airway management, that are applied to a wide range of ill and injured
FIGURE 1  Distribution of ICU-free days among patient subgroups. Each panel shows ICU-free days by treatment group, either BVM or ETI. The leftmost panel in the top row shows the overall comparison of ICU-free days between the BVM and ETI treatment groups. The overall comparison of BVM versus ETI was not significant ($P = 0.219$). Remaining panels show the BVM versus ETI comparison within a subgroup. BVM, bag-valve-mask-ventilation; ETI, endotracheal intubation; SIDS, sudden infant death syndrome.

TABLE 3  ICU-free days by neurologic outcome

| Neurologic outcome                  | BVM (n = 404) | ETI (n = 416) |
|------------------------------------|---------------|---------------|
|                                    | No. of patients | ICU-free days median (IQR) | No. of patients | ICU-free days median (IQR) |
| Normal or no change from baseline  | 72            | 29 (27.2–30)  | 58            | 28 (23–29)  |
| Mild disability                    | 20            | 27 (22.5–29)  | 27            | 24.5 (18.2–28)  |
| Moderate disability                | 6             | 14.5 (5.7–20.2) | 7             | 19 (6–22.5)  |
| Severe disability                  | 10            | 13 (0–14.7)   | 6             | 21.5 (17.2–25)  |
| Coma/vegetative                    | 15            | 10 (0–15)     | 12            | 8.5 (0.75–16.2)  |
| Death                              | 281           | 0 (0)         | 306           | 0 (0)         |

Abbreviations: BVM, bag-valve-mask ventilation; ETI, endotracheal intubation; IQR, interquartile range.

patients. Broad inclusion criteria are desirable since specific subgroups of critically ill children are rare, limiting the feasibility of conducting studies targeted to specific populations. Further, the number of ICU-free days can be objectively derived from health records, with little interpretation, resulting in high interrater reliability. By assigning zero ICU-free days to patients who die, regardless of whether there is a period during which they are alive and out of the ICU, the potential limitation associated with competing risks in composite endpoints is addressed.\(^{29}\) Otherwise, a patient who dies quickly in the ICU and thus has a short ICU stay would be assigned a favorable outcome identical to a patient who recovers quickly and is discharged home.

We have evaluated ICU-free days as an alternative outcome using data from a previous controlled trial of BVM versus ETI in the pre-hospital care of critically ill and injured children. The original study captured both in-hospital mortality and the neurologic outcomes of enrolled subjects at hospital discharge. Thus, the dataset provides a
powerful tool with which to compare the ICU-free days endpoint to well-accepted and clinically relevant outcomes in pediatric critical care. ICU-free days as a clinical outcome was able to capture both survival and neurological outcome utilizing a single outcome. In comparison, the original trial expressed this outcome separately as survival (BVM: 30% vs ETI: 26%) and good neurologic outcome (BVM: 23% vs ETI: 20%). Furthermore, we found that ICU-free days appeared to be a more sensitive measure of treatment effect, as reflected by a larger number of statistically significant treatment effects in patient subgroups (child maltreatment, foreign body aspiration, and respiratory arrest), than either of the prior endpoints alone. In contrast, the previous trial showed differences in survival for the child maltreatment (BVM: 42% vs ETI: 5%) and respiratory arrest subgroups (BVM: 85% vs ETI: 61%) and in neurologic outcome in the foreign body subgroup (BVM: 69% vs ETI: 23%). This difference with the original trial suggests that the endpoint of ICU-free days may be a practical, sensitive, and more powerful single measure of treatment effects (ie, allowing for reduced numbers of patients in subgroups while maintaining the power to detect differences in outcome) in evaluating the prehospital care of critically ill and injured infants and children.

In conclusion, based on a secondary analysis of data from a prospective clinical trial, we found ICU-free days to be an appropriate primary endpoint for well-accepted outcomes in EMS research in the pediatric population. ICU-free days may be more sensitive than either mortality or PCPC scores alone in identifying treatment effects in the prehospital care of critically ill children, compared to either a simple mortality endpoint or an endpoint based on the PCPC.

In conclusion, based on a secondary analysis of data from a prospective clinical trial, we found ICU-free days to be an appropriate primary endpoint for well-accepted outcomes in EMS research in the pediatric population. ICU-free days may be more sensitive than either mortality or PCPC scores alone in identifying treatment effects in the prehospital care of critically ill children, compared to either a simple mortality endpoint or an endpoint based on the PCPC.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

REFERENCES
1. Reis AG, Nadkarni V, Perondi MB, Grisi S, Berg RA. A prospective investigation into the epidemiology of in-hospital pediatric cardiopulmonary resuscitation using the international Utstein reporting style. Pediatrics. 2002;109(2):200-209.
2. Gausche M, Lewis RJ, Stratton SJ, et al. Effect of out-of-hospital pediatric endotracheal intubation on survival and neurological outcome: a controlled clinical trial. JAMA. 2000;283(6):783-790.
3. Gausche-Hill M, Lewis RJ, Gunter CS, Henderson DP, Haynes BE, Stratton SJ. Design and implementation of a controlled trial of pediatric endotracheal intubation in the out-of-hospital setting. Ann Emerg Med. 2000;36(4):356-365.
4. Sayre MR, Gausche-Hill M. Conducting randomized trials in the prehospital setting. Prehosp Emerg Care. 2009;6(sup2):S38-S47.
5. Lipsky AM, Gausche-Hill M, Vienna M, Lewis RJ. The importance of “shrinkage” in subgroup analyses. Ann Emerg Med. 2010;55(6):544-552.e3.
6. Wang HE, Schmicker RH, Daya MR, et al. Effect of a strategy of initial laryngeal tube insertion vs endotracheal intubation on 72-hour survival in adults with out-of-hospital cardiac arrest: a randomized clinical trial. JAMA. 2018;320(8):769-778.
7. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Canadian Association of Caribbean States, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation. 2015;96:328-340.
8. Fiser DH, Long N, Roberson PK, Heffley G, Zolten K, Brodie-Fowler M. Relationship of pediatric overall performance category and pediatric cerebral performance category scores at pediatric intensive care unit discharge with outcome measures collected at hospital.
discharge and 1- and 6-month follow-up assessments. Crit Care Med. 2000;28(7):2516-2620.

9. Kirschen MP, Topjian AA, Hammond R, Illes J, Abend NS. Neuroprognostication after pediatric cardiac arrest. Pediatr Neurol. 2014;51(5):663-668.e2.

10. Zaritsky A, Nadkarni V, Hazinski MF, et al. Recommended guidelines for uniform reporting of pediatric advanced life support: the pediatric Utstein Style. A statement for healthcare professionals from a task force of the American Academy of Pediatrics, the American Heart Association, and the European Resuscitation Council. Circulation. 1995;92(7):2006-2020.

11. Laupland KB, Kirkpatrick AW, Kortbeek JB, Zuege DJ. Long-term mortality outcome associated with prolonged admission to the ICU. Chest. 2006;129(4):954-959.

12. Kisat MT, Latif A, Zogg CK, et al. Survival outcomes after prolonged intensive care unit length of stay among trauma patients: the evidence for never giving up. Surgery. 2016;160(3):771-780.

13. Fernando SM, Reardon PM, Bagshaw SM, et al. Impact of nighttime rapid response team activation on outcomes of hospitalized patients with acute deterioration. Crit Care. 2018;22(1):67.

14. Makhoul N, Khamisy-Farah R, Farah R. Length of stay and outcome of hospitalized chronic obstructive pulmonary disease patients, differences between general medical ward and intensive care unit: a cohort study. West Indian Med J. 2013;62(8):738-743.

15. Hughes M, Grant IS. Outcome of long-stay intensive care patients. Intensive Care Med. 2001;27(4):779-782.

16. Heyland DK, Konopad E, Noseworthy TW, Johnston R, Gafni A. Is it “worthwhile” to continue treating patients with a prolonged stay (>14 days) in the ICU? An economic evaluation. Chest. 1998;114(1):192-198.

17. Fernando SM, Reardon PM, Scales DC, et al. Prevalence, risk factors, and clinical consequences of recurrent activation of a rapid response team: a multicenter observational study. J Intensive Care Med. 2019;34(10):782-789.

18. Lazaridis C, Yang M, DeSantis SM, Luo ST, Robertson CS. Predictors of intensive care unit length of stay and intracranial pressure in severe traumatic brain injury. J Crit Care. 2015;30(6):1258-1262.

19. Kurek Eken M, Tüten A, Özkaya E, Karatekin G, Karateke A. Major determinants of survival and length of stay in the neonatal intensive care unit of newborns from women with premature preterm rupture of membranes. J Matern Fetal Neonatal Med. 2017;30(16):1972-1975.

20. Becker GJ. Outcome and cost of prolonged stay in the surgical intensive care unit. Arch Surg. 1984;119(11):1338.

21. Moissey LL, Mourtzakis M, Cotton BA, et al. Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. Crit Care. 2013;17(5):R206.

22. Dulhunty JM, Roberts JA, Davis JS, et al. A protocol for a multicentre randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients with severe sepsis: the BLING II study. Crit Care Resusc. 2013;15(3):179-185.

23. Young P, Hodgson C, Dulhunty J, et al. End points for phase II trials in intensive care: recommendations from the Australian and New Zealand Clinical Trials Group consensus panel meeting. Crit Care Resusc. 2012;14(3):211-215.

24. Geneslaw AS, Jia H, Lucas AR, Agus MS, Edwards JD. Pediatric intermediate care and pediatric intensive care units: pICU metrics and an analysis of patients that use both. J Crit Care. 2017;41:268-274.

25. Gupta P, Gossett J, Rao Rettiganti M. Trends in mortality rates in pediatric intensive care units in the United States from 2004 to 2015. Crit Care Med. 2018;46(1):30.

26. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med. 2017;376:318-329.

27. Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (randomized embedded multifactorial adaptive platform for community-acquired pneumonia) study. Rationale and design. Ann Am Thorac Soc. 2020;17:879-891.

28. Irony TZ. The “utility” in composite outcome measures: measuring what is important to patients. JAMA. 2017;318(18):1820-1821.

AUTHOR BIOGRAPHY

Hanjin Cho, MD, PhD, is a Professor of Emergency Medicine at Korea University College of Medicine, Seoul, Korea.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.