Journal of the American Heart Association

ORIGINAL RESEARCH

Characterization of "ICU-30": A Binary Composite Outcome for Neonates With Critical Congenital Heart Disease

Monique M. Gardner, MD; Garrett Keim, MD; Jill Hsia, MD; Anh D. Mai, MS; J. William Gaynor, MD; Andrew C. Glatz, MD, MSCE; Nadir Yehya, MD, MSCE

BACKGROUND: Neonates with heart disease requiring cardiopulmonary bypass surgery are at high risk for mortality and morbidity. As it is rare, short-term mortality is difficult to use as a primary outcome for clinical studies. We proposed "ICU-30" as a binary composite "poor" outcome consisting of: (1) mortality within 30 days, (2) intensive care unit (ICU) admission ≥30 days, or (3) ICU readmission before day 30. To measure the utility of this composite, we assessed its prognostic properties for 6- and 12-month mortality.

METHODS AND RESULTS: This was a retrospective single-center cohort study of neonates requiring cardiopulmonary bypass between 2013 and 2020. Mortality among patients with and without the ICU-30 outcome was compared using log-rank tests and Cox regression. Areas under the receiver operating characteristic curves assessed the ability of the composite to predict 12-month mortality. In 887 neonates, 232 (26.2%) experienced the ICU-30 outcome, with more prolonged ICU stays and readmissions (both ≥9%) than 30-day mortality (4.2%). ICU-30 was associated with higher rates of 6- and 12-month mortality (log-rank $P<0.001$) and predicted 12-month mortality with area under the receiver operating characteristic of 0.81 (95% CI, 0.77–0.85). In 30-day survivors, both prolonged ICU stay (hazard ratio, 12.3; 95% CI, 6.70–22.7; $P<0.001$) and ICU readmission (hazard ratio, 2.99; 95% CI, 1.17–7.63; $P=0.02$) were associated with 12-month mortality.

CONCLUSIONS: ICU-30, a composite outcome of mortality, ICU length of stay, or ICU readmission by 30 days was associated with 6- and 12-month mortality in neonates requiring cardiopulmonary bypass. ICU-30 is captured in routine data collection and appears to be a valid binary patient-centered outcome.

Key Words: congenital heart disease ■ mortality ■ neonatal cardiopulmonary bypass ■ outcomes

Neonates with critical congenital heart disease requiring surgery in the first month of life are at high risk for morbidity and mortality after cardiopulmonary bypass (CPB) surgery, with a 30-day postoperative mortality rate of 5% to 11% for the most complex neonatal operations.[1] While mortality is clearly an unwanted outcome, an ≈10% postoperative rate is still relatively rare for use as an outcome for clinical studies. Mortality at 6 and 12 months of age is higher and would be more useful for powering studies, but is impractical for perioperative studies, as it adds the additional burdens associated with long-term assessments, including loss to follow-up. Furthermore, longer-term mortality is less impacted by perioperative interventions, risking bias if used as a primary outcome to assess perioperative exposures. When developing an outcome for intensive care unit (ICU) therapies and interventions, it is therefore important to have a practical and valid short-term outcome, with an event rate that occurs with enough frequency to allow for adequate statistical analysis. Ideally, this outcome would also serve as an accurate

Correspondece to: Monique M. Gardner, MD, The Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, 8NE Main Building, Office 8556, Philadelphia, PA 19104. Email: gardnerm@chop.edu

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.025494

For Sources of Funding and Disclosures, see page 7.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Neonates requiring cardiopulmonary bypass for congenital heart disease in the first weeks of life have worse outcomes compared with older children, but mortality is not the only marker for poor outcome.
- ICU-30, a composite outcome of mortality, intensive care unit length of stay, or intensive care unit readmission by 30 days is substantially more prevalent than mortality alone and is associated with 6- and 12-month mortality.

What Are the Clinical Implications?

- Novel composite outcome measures such as ICU-30 that are easily abstracted through standardly collected data and patient-centered may be helpful in clinical research in this patient population.

Nonstandard Abbreviations and Acronyms

CPB	cardiopulmonary bypass
ICU-30	a novel outcome measure consisting of mortality, ICU length of stay, or ICU readmission by 30 days

surrogate of later outcomes that providers and families care about.

Other measures of short-term outcome after CPB have included ICU length of stay[2] and hospital readmissions, but it is unclear how prognostic or patient-centered these metrics are. Adult studies have used days alive out-of-hospital[3,4]; however, days alive out-of-hospital–type metrics have not been robustly examined in children. In neonatal congenital heart disease, existing composites have focused on combinations of mortality and surgical complications and have been used primarily for center-level risk-adjustment.[5,6] These also have not been demonstrated to be patient-centered nor predictive of longer-term outcomes.

In a recent observational cohort study requiring a binary outcome, we proposed a composite "poor" outcome, named "ICU-30", consisting of: (1) mortality within 30 days, (2) index ICU length of stay (LOS) ≥30 days, and (3) ICU readmission (either from step-down unit or outpatient readmission) by day 30. This metric represents a binary version of days alive out-of-ICU by day 30, with penalization for ICU readmission. The properties of the ICU-30 composite are unknown. To better characterize the clinical relevance of our composite, we assessed its prognostic properties in a larger cohort. We hypothesized that this ICU-30 "poor outcome" could identify infants with higher mortality at 6 and 12 months of age and could serve as a valid patient-centered outcome for future research.

METHODS

This was a retrospective single-center cohort study of all neonates requiring CPB between 2013 and 2020. This study was reviewed and deemed exempt from obtaining informed consent by the Children's Hospital of Philadelphia Institutional Review Board (IRB 21-019026). The Children's Hospital of Philadelphia Cardiac Center's surgical database was screened for neonates <30 days of age requiring CPB for congenital heart disease as their index operation. Demographic, preoperative, and postoperative events and vital status at 30 days, 6 months, and 12 months were collected from the electronic medical record though highly validated data collected for other cardiac registries including the Society of Thoracic Surgery and Pediatric Cardiac Critical Care Consortium. All patients had follow-up through 1 year of age through the Cardiac Center's robust appointment and telephonic follow-up. Thirty-day ICU readmissions were reviewed and categorized into readmission after: unplanned cardiac operation, unplanned cardiac catheterization, cardiac arrest, cardiorespiratory-medical admission, and non-cardiac admission. For those who died within 12 months, cause of death was categorized into: cardiac arrest, cardiogenic shock with multisystem organ failure, respiratory failure, neurologic failure, or an out-of-hospital event that could not be characterized. Results are reported in n (%) or median (interquartile range), and subjects with or without the ICU-30 outcome were compared with Chi-square or Wilcoxon rank sum tests. Kaplan–Meier curves were graphed, censored at 365 days, and compared with log-rank test. We tested the relative contribution of the elements of the composite on 12-month mortality using Cox regression. Areas under the receiver operating characteristic (AUROC) curves were used to assess the ability of the composite to predict 12-month mortality. We also performed a sensitivity analysis with the creation of AUROC curves limited to subjects with surgery before March 2020 because of the COVID-19 pandemic. Other variables were iteratively added to the composite definition to assess whether the AUROC improved. Statistical analysis was performed with Stata SE Release 16 (College Station, TX: StataCorp LP). All supporting data are available within this article and the supplemental material.

RESULTS

Our cohort included 887 neonates, with 232 (26.2%) experiencing the ICU-30 composite outcome, with twice as many prolonged ICU stays and readmissions (both ≥9%) than 30-day non-survivors (4.2%) (Tables 1 and 2). Infants with the ICU-30 outcome had a younger gestational age (P<0.0001), were more likely to have a genetic syndrome (P<0.0001) or chromosomal abnormality (P=0.004) and were more likely to have a higher STAT (Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery) category operation (P<0.0001). Postoperative events included higher rates of delayed sternal closure, renal replacement therapy, cardiac arrest, extracorporeal support (extracorporeal membrane oxygenation) need, and seizures in neonates with poor outcome (all P<0.001). Of those with the ICU-30 outcome at 30 days, 68 (29%) had died by 6 months, and 72 (31%) by 12 months, compared with the group without a composite poor outcome (1.8% and 2.4% mortality at 6 and 12 months, respectively, both P<0.001). Cardiac arrest and cardiogenic shock with multisystem organ failure were the most common cause for mortality at 30 days, 6 and 12 months (Table S1). When restricting the cohort to 30-day survivors with poor outcome, 31 (15.9%) and 35 (17.9%) subjects had died by 6 and 12 months, respectively, both of which were higher in those with ICU-30 outcome than those without (P<0.001).

In efforts to understand the mechanisms contributing to the ICU-30 outcome, we categorized the causes for 30-day mortality (Table S1), prolonged ICU LOS (Table S2), and ICU readmission (Table S3). Most patients were readmitted to the cardiac ICU for a cardiac-medical reason (47.1%), which included increased respiratory support or initiation of vasoactive medications, or after cardiac re-operation (23.5%) including cardiopulmonary bypass and sternal wound procedures (Table S3).

Having the ICU-30 outcome predicted 12-month mortality with an AUROC of 0.81 (95% CI, 0.77–0.85) (Table 3, Table S4). As this study overlapped the beginning of the COVID-19 pandemic, sensitivity analysis revealed no change in the AUROC with a cohort limited to those with surgery before March 2020 (n=820, AUROC, 0.81 [95% CI, 0.76–0.85]). Modifying the definition of the composite outcome to also include other postoperative events including renal replacement therapy, extracorporeal membrane oxygenation, cardiac arrest, and seizures demonstrated only marginal increase in the number of subjects not captured in the initial definition (+1, +24, +12, and +33 subjects, respectively), with no substantial difference in the number of 12-month nonsurvivors (0, +1, +1, +3) (Table 3). The AUROC was not improved with the addition of any of these variables to the composite.

Kaplan–Meier curves (Figure 1) demonstrated a significant difference in 12-month mortality between those with and without the ICU-30 outcome (log-rank P<0.001). Evaluation of the components of the composite outcome in 30-day survivors (Figure 2) showed prolonged ICU LOS ≥30 days with a hazard ratio of 12.34 (95% CI, 6.70–22.72; P<0.001) for 12-month mortality, and ICU readmission with a hazard ratio of 2.99 (95% CI, 1.17–7.63; P=0.02).

DISCUSSION

ICU-30, a composite outcome of 30-day mortality, prolonged ICU length of stay ≥30 days, or ICU readmission by day 30 was associated with 6- and 12-month mortality in neonates requiring CPB for critical congenital heart disease. The ICU-30 outcome identified a cohort of neonates with greater perioperative risk factors, more interventions, and worse short- and long-term outcomes. Higher 12-month mortality was driven by subjects with ≥30-day index ICU LOS, although ICU readmission by day 30 was also significantly associated with mortality. This composite poor outcome appears to be valid, patient-centered, easily obtained from administrative data in a short observation period postoperatively, occurs with a reasonably high frequency, and is potentially useful as a primary outcome for studies in critically ill neonates requiring CPB.

As mortality for the most complex neonatal operations has decreased over the past 20 years,[1,7] observational and interventional studies require ever larger cohorts to identify effects on this outcome. Surrogate short-term outcomes should ideally be associated with important longer-term outcomes and measured with high fidelity. Alternative outcomes have been considered in other disease processes, such as sepsis,[8,9] as mortality is both infrequent and not necessarily the only measure of importance. This issue is especially important in pediatrics, and particularly pediatric cardiology and critical care, where both disease prevalence and mortality are rare, with studies in the past underpowered to measure mortality differences.[10–12] In other pediatric critical illness syndromes, short-term surrogate outcomes have been critiqued for inadequate assessment for whether they correlate with longer-term morbidity or mortality,[9] calling into question their utility, validity, and patient-centeredness. Our composite poor outcome at 30 days predicted 6- and 12-month mortality, thus providing criterion validity for its use.

In adults, the outcome of days alive out-of-hospital after cardiac intervention has been demonstrated to be an important patient-centered outcome[4]; it is more recently being explored in pediatric cardiology.[13] Our ICU-30 outcome functionally creates a binary version

Table 1. Demographics of Neonates Requiring CPB (n=887)

	Total cohort (n=887)	ICU-30 outcome (n=232)	Without ICU-30 outcome (n=655)	*P* value
Sex				0.707
Female	354 (39.9%)	95 (40.9%)	259 (39.5%)	
Male	533 (60.1%)	137 (59.1%)	396 (60.5%)	
Race				0.224
White	522 (59.9%)	123 (53.0%)	399 (60.9%)	
Black	97 (10.9%)	25 (10.8%)	72 (11.0%)	
Multiracial	41 (4.6%)	11 (4.7%)	30 (45.8%)	
Asian, Indian, Pacific Islander	23 (2.6%)	7 (3.0%)	16 (2.4%)	
Other or refused	204 (23.0%)	66 (28.4%)	138 (21.1%)	
Ethnicity				0.026
Non-Hispanic/ non-Latino	743 (83.8%)	182 (78.4%)	561 (87.6%)	
Hispanic/Latino	138 (15.6%)	47 (20.3%)	91 (14.9%)	
Refused	6 (0.6%)	3 (1.3%)	3 (0.5%)	
Gestational age, wk	39 (38, 39)	38 (37, 39)	39 (38, 39)	<0.001
Genetic syndrome	187 (21.1%)	117 (50.4%)	70 (10.7%)	<0.001
Chromosomal abnormality	242 (27.3%)	80 (34.5%)	162 (24.7%)	0.004
Age at surgery, d	5 (3, 7)	5 (3, 10.5)	5 (3, 6)	0.005
Initial CPB surgery				<0.001
STAT 1	8 (0.9%)	3 (1.3%)	5 (0.8%)	
STAT 2	47 (5.3%)	15 (6.5%)	32 (4.9%)	
STAT 3	165 (18.6%)	17 (7.3%)	148 (22.6%)	
STAT 4	417 (47.1%)	109 (47.0%)	308 (47.0%)	
STAT 5	249 (28.1%)	87 (37.5%)	162 (24.7%)	
Year of surgery				0.876
2013	117 (13.2%)	33 (14.2%)	84 (12.8%)	
2014	112 (12.6%)	29 (12.5%)	83 (12.7%)	
2015	111 (12.5%)	32 (13.8%)	79 (12.1%)	
2016	114 (12.9%)	24 (10.3%)	90 (13.7%)	
2017	134 (15.1%)	32 (13.8%)	102 (15.6%)	
2018	106 (12.0%)	28 (12.1%)	78 (11.9%)	
2019	106 (12.0%)	31 (12.4%)	75 (11.5%)	
2020	87 (9.8%)	23 (9.9%)	64 (9.8%)	
Delayed sternal closure	269 (30.3%)	119 (51.3%)	150 (22.9%)	<0.001
RRT within 30 d	8 (0.9%)	7 (3.0%)	1 (0.2%)	<0.001
Cardiac arrest within 48 h	27 (3.0%)	15 (6.5%)	12 (1.8%)	<0.001
ECMO within 48 h	97 (10.9%)	73 (31.5%)	24 (3.7%)	<0.001
Seizures within 48 h	85 (9.6%)	49 (21.1%)	36 (5.5%)	<0.001
CICU length of stay, d	11.6 (8, 18.8)	23.7 (8.7, 42.4)	11.0 (8.0, 15.5)	<0.001
Mortality within 30 d	37 (4.2%)	37 (15.9%)	0	<0.001
Mortality within 6 mo	80 (9.0%)	68 (29.3%)	12 (1.8%)	<0.001
Mortality within 12 mo	88 (9.9%)	72 (31.0%)	16 (2.4%)	<0.001
Mortality within 6 mo in 30-d survivors (n=850)	43 (5.1%)	31 (15.9%)	12 (1.8%)	<0.001
Mortality within 12 mo in 30-d survivors (n=850)	51 (6.0%)	35 (17.9%)	16 (2.4%)	<0.001

Results presented as n (%) or median (interquartile range). Comparisons made with Chi-square test and Wilcoxon ranksum between Composite and No Composite groups. CICU indicates cardiac intensive care unit; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy; and STAT, Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery classification.

Table 2. Summary of Composite ICU-30 Outcome Breakdown

Prolonged CICU LOS (≥30 d)	110 (12.5%)
Mortality within 30-d	37 (4.2%)
CICU readmission	85 (9.6%)
Composite outcome	232 (26.2%)

Results presented as n (%). ICU-30 outcome is categorrized as either 30-day mortality, prolonged ICU LOS ≥30 days, or CICU readmission within 30 days. CICU indicates cardiac intensive care unit; and LOS, length of stay.

of days-alive-out-of-ICU in the first 30 days for neonates with critical congenital heart disease, accounting and penalizing for readmissions to the ICU. The ICU-30 outcome scores 30-day non-survivors, 30-day LOS, and 30-day readmissions as having 0 days-alive-out-of-ICU. Given the acceptance of days alive out-of-hospital and ICU-free days as composite outcomes in cardiology[14–16] and critical illness,[17] our ICU-30 binary composite provides a potential short-term validated surrogate for subjects in neonatal cardiac ICU. Its construct as a binary variable is particularly helpful in some analyses, such as for predictive models.[18–20] We propose further exploration of this outcome in pediatric cardiac critical care as it could aid in future clinical trial design.

The components of the ICU-30 outcome, primarily prolonged LOS, have been explored in other pediatric cardiology studies. Prolonged ICU LOS is an important outcome and one that is increasing as medical complexity increases.[2,21] Prolonged ICU LOS has been shown to be associated with 12-month mortality in children with congenital heart disease previously,[22] consistent with this component driving the association with 12-month mortality in our study. Hospital readmissions, the final component of our ICU-30 composite, are relatively common after congenital heart disease operations,[23,24] especially in the most high-risk neonates with single ventricle heart disease.[25,26] However, ICU readmissions have not been robustly studied as a contributor to longer-term outcomes. Both prolonged index ICU LOS and ICU readmission, together with mortality, contribute to days alive out of ICU. In our study, 30-day readmission was associated, albeit not as robustly as LOS ≥30 days, with 12-month mortality, suggesting that short-term readmission itself has prognostic significance. Most of the readmission events were because of cardiopulmonary decompensations or unplanned cardiac surgeries and catheterizations suggesting continued cardiac-related morbidity even in those patients who survived and were discharged from the cardiac ICU. As cardiac etiologies are the most common reason for mortality, our ICU-30 outcome may serve as a surrogate for significant continued cardiac disease, yielding some early insight in the mechanistic relationship between the composite components and the outcome of mortality.

With an event rate of about one-quarter of patients in this large cohort, the ICU-30 outcome is a relatively frequent event that is easily captured in the first 30 days of a neonates' course, with factors that are easily recorded in large databases, including Society of Thoracic Surgery[27,28] and Pediatric Cardiac Critical Care Consortium.[29–31] The strong association of the ICU-30 outcome with mortality at 6- and 12-months also raises the possibility of additional counseling and resources for providers and families, as well providing a framework for investigating the modifiable risk factors driving higher medium- and long-term mortality.

In addition to mortality and LOS, outcomes studied in pediatric critical care have also included postoperative reintervention, duration of mechanical ventilation, reintubation rates, and accumulation of new morbidities.[32–37] We did not find improvement in our definition of poor composite outcome when adding cardiac arrest, extracorporeal membrane oxygenation, renal replacement therapy, or seizures. Patients requiring resuscitation[38] and extracorporeal membrane oxygenation [39,40] were likely to have high rates of mortality or prolonged ICU LOS, so the lack of improvement of AUROC with the addition of these factors likely represents collinearity. Seizures, routinely measured at our center for all neonates after CPB, is a potentially important outcome.[41] However, at a prevalence of 10%, it is frequent but not always associated with short- or long-term mortality, and its inclusion as a "patient-centered" outcome is uncertain. Additionally, seizures are not routinely measured at many centers, and thus including it in the definition would limit utility of this composite outcome at other centers or in most large databases.

Table 3. Twelve-Month Mortality Counts and AUROC Curves With Added Outcomes to Composite

	Count	Total	12-mo mortality	AUROC	95% CI
Composite	…	232	72	0.81	0.76–0.85
+ RRT	8	233 (+1)	72 (0)	0.81	0.77–0.85
+ ECMO	97	256 (+24)	73 (+1)	0.81	0.76–0.84
+ CPR	27	244 (+12)	73 (+1)	0.81	0.77–0.85
+ Seizures	85	268 (+33)	75 (+3)	0.81	0.77–0.85

AUROC indicates area under the receiver operating characteristic; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; and RRT, renal replacement therapy.

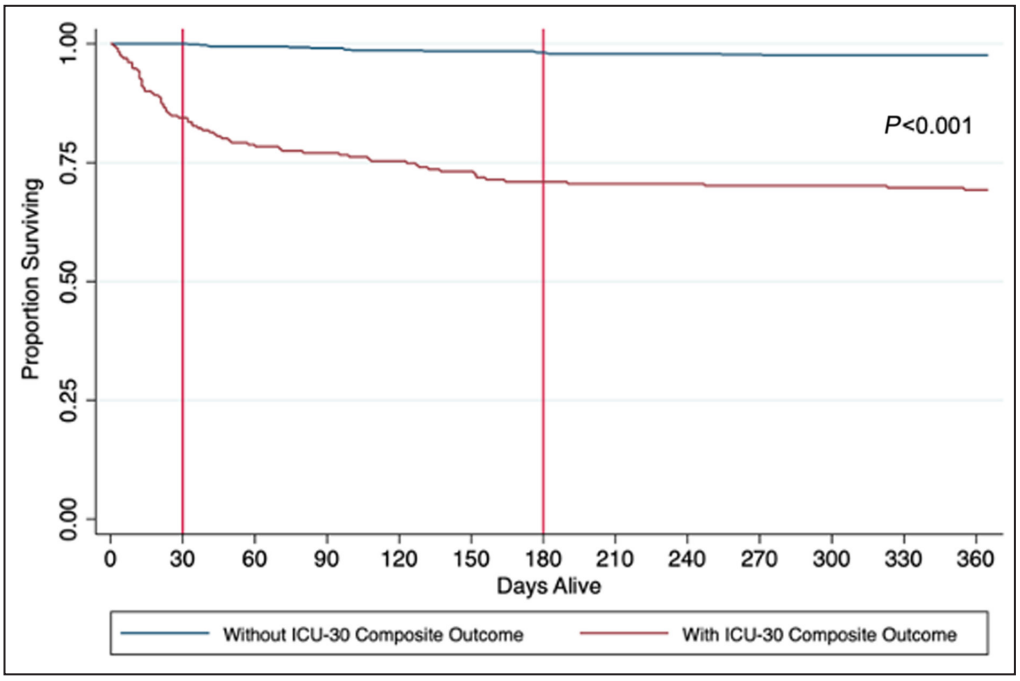

Figure 1. Kaplan–Meier curves by ICU-30 composite outcome.
Lines at 30 days and 6 months demarcating time points of interest. Curves compared with log-rank sum (P<0.001). ICU-30 outcome is categorrized as either 30-day mortality, prolonged ICU LOS ≥30 days, or CICU readmission within 30 days.

Our study has limitations. This was single-center data and will thus have to be examined for generalizability

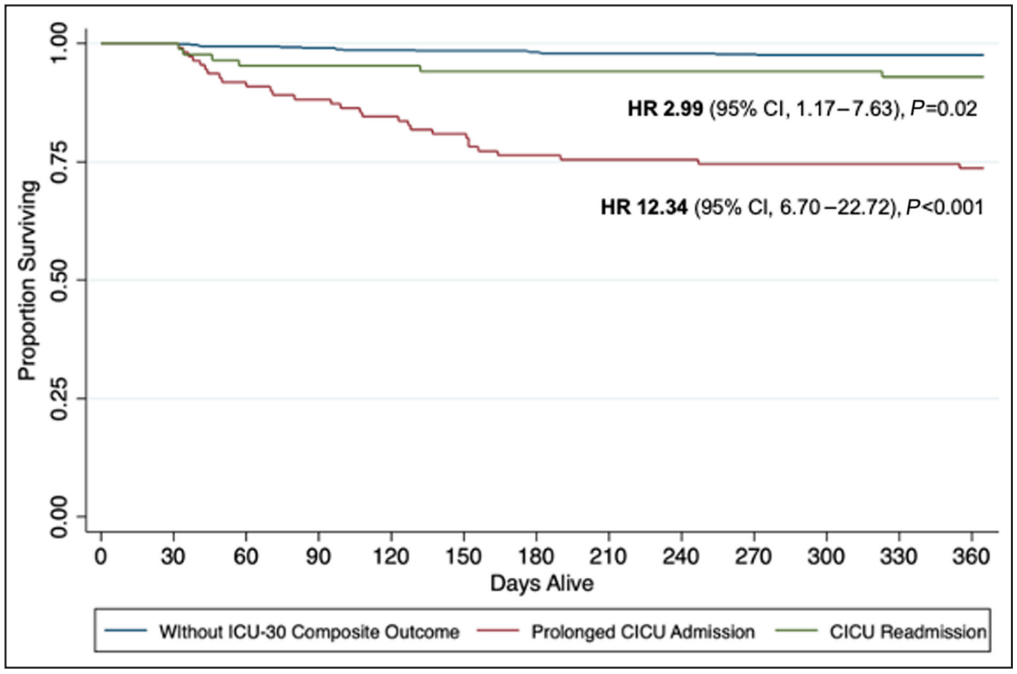

Figure 2. Kaplan–Meier curves in 30-day survivors based on component of ICU-30 composite outcome.
Hazard ratios for prolonged intensive care unit admission and intensive care unit readmission were calculated with Cox regression. CICU indicates cardiac intensive care unit; HR, hazard ratio.ICU-30 outcome is categorrized as either 30-day mortality, prolonged ICU LOS ≥30 days, or CICU readmission within 30 days.

with larger multicenter databases. Center-level practice variations could contribute to different frequencies of mortality, prolonged ICU LOS, and readmission, including care of neonates outside of the cardiac ICU (neonatal units). We did not consider a broader pediatric cardiac ICU population, but limited our analysis to neonates requiring CPB, which also may limit generalizability. However, this cohort represents a high-risk cohort, which would likely drive the prevalence of poor outcome in any cardiac ICU, warranting the specific focus. Finally, while our broad categorization for causes of mortality, prolonged LOS, and readmission are incomplete in identifying a direct mechanism linking prolonged ICU LOS or readmissions with 6- and 12-month mortality, our findings are suggestive of continued significant cardiac disease in patients with the composite outcome.

CONCLUSIONS

ICU-30, a composite outcome of 30-day mortality, prolonged ICU LOS ≥30 days and ICU readmission by day 30 was associated with 6- and 12-month mortality in neonates requiring CPB for critical congenital heart disease. The ICU-30 outcome allows for a binary categorization of patients and is easily captured with high relatability in data collection. This construct found prolonged LOS as the primary driver of the association with 12-month mortality, with penalties for 30-day mortality and early readmission. This composite appears to be a valid patient-centered outcome for critically ill neonates undergoing congenital heart disease surgery.

ARTICLE INFORMATION

Received February 1, 2022; accepted May 3, 2022.

Affiliations

Division of Cardiac Critical Care, Department of Anesthesiology and Critical Care (M.M.G.), Division of Critical Care, Department of Anesthesiology and Critical Care (G.K., N.Y.), Division of Cardiology, Department of Pediatrics (J.H., A.D.M.), Division of Cardiothoracic Surgery, Department of Surgery (J.W.G.), Division of Cardiology, Department of Pediatrics (A.C.G.); and Center for Pediatric Clinical Effectiveness (A.C.G.), The Children's Hospital of Philadelphia, Philadelphia, PA; and Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA (N.Y.).

Acknowledgments

We want to specifically acknowledge the tireless work of Andrea Kennedy, Lead Clinical Data Management Specialist for the Cardiac Center at the Children's Hospital of Philadelphia. For this study, we appreciate the time and effort of Jenny (Yeon Jae) Shin for her contribution to obtaining data.

Sources of Funding

This research required no funding or grant support.

Disclosures

None of the authors have disclosures to report.

Supplemental Material

Tables S1–S4

REFERENCES

1. Jacobs JP, He X, Mayer JE, Austin EH III, Quintessenza JA, Karl TR, Vricella L, Mavroudis C, O'Brien SM, Pasquali SK, et al. Mortality trends in pediatric and congenital heart surgery: an analysis of the society of thoracic surgeons congenital heart surgery database. *Ann Thorac Surg*. 2016;102:1345–1352. doi: 10.1016/j.athoracsur.2016.01.071
2. DeWitt AG, Rossano JW, Bailly DK, Bhat PN, Chanani NK, Kirkland BW, Moga MA, Owens GE, Retzloff LB, Zhang W, et al. Predicting and surviving prolonged critical illness after congenital heart surgery. *Crit Care Med*. 2020;48:e557–e564. doi: 10.1097/CCM.0000000000004354
3. Ariti CA, Cleland JGF, Pocock SJ, Pfeffer MA, Swedberg K, Granger CB, McMurray JJV, Michelson EL, Östergren J, Yusuf S, et al. Days alive and out of hospital and the patient journey in patients with heart failure: insights from the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program. *Am Heart J*. 2011;162:900–906. doi: 10.1016/j.ahj.2011.08.003
4. Fanaroff AC, Cyr D, Neely ML, Bakal J, White HD, Fox KAA, Armstrong PW, Lopes RD, Ohman EM, Roe MT, et al. Days alive and out of hospital: exploring a patient-centered, pragmatic outcome in a clinical trial of patients with acute coronary syndromes. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004755. doi: 10.1161/CIRCOUTCOMES.118.004755
5. O'Brien SM, Jacobs JP, Shahian DM, Jacobs ML, Gaynor JW, Romano JC, Gaies MG, Hill KD, Mayer JE, Pasquali SK, et al. Development of a congenital heart surgery composite quality metric: part 2—analytic methods. *Ann Thorac Surg*. 2019;107:590–596. doi: 10.1016/j.athoracsur.2018.07.036
6. Pasquali SK, Shahian DM, O'Brien SM, Jacobs ML, Gaynor JW, Romano JC, Gaies MG, Hill KD, Mayer JE, Jacobs JP, et al. Development of a congenital heart surgery composite quality metric: part 1—conceptual framework. *Ann Thorac Surg*. 2019;107:583–589. doi: 10.1016/j.athoracsur.2018.07.037
7. Mascio CE, Irons ML, Ittenbach RF, Gaynor JW, Fuller SM, Kaplinski M, Kennedy AT, Steven JM, Nicolson SC, Spray TL, et al. Thirty years and 1663 consecutive Norwood procedures: has survival plateaued? *J Thorac Cardiovasc Surg*. 2019;158:220–229. doi: 10.1016/j.jtcvs.2018.12.117
8. Graf J, Doig GS, Cook DJ, Vincent JL, Sibbald WJ. Randomized, controlled clinical trials in sepsis: has methodological quality improved over time? *Crit Care Med*. 2002;30:461–472. doi: 10.1097/00003246-200202000-00032
9. Curley MAQ, Zimmerman JJ. Alternative outcome measures for pediatric clinical sepsis trials. *Pediatr Crit Care Med*. 2005;6:S150–S156. doi: 10.1097/01.PCC.0000161582.63265.B6
10. Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, Canter CE, Mahony L, Ross RD, Pahl E, Blume ED, Dodd DA, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA*. 2007;298:1171–1179. doi: 10.1001/jama.298.10.1171
11. Day RW, Hawkins JA, McGough EC, Crezeé KL, Orsmond GS. Randomized controlled study of inhaled nitric oxide after operation for congenital heart disease. *Ann Thorac Surg*. 2000;69:1907–1912; discussion 1913. doi: 10.1016/S0003-4975(00)01312-6
12. Jain A, Oster M, Kilgo P, Grudziak J, Jokhadar M, Book W, Kogon BE. Risk factors associated with morbidity and mortality after pulmonary valve replacement in adult patients with previously corrected tetralogy of Fallot. *Pediatr Cardiol*. 2012;33:601–606. doi: 10.1007/s00246-012-0185-z
13. Nathan M, Trachtenberg FL, Van Rompay MI, Gaynor W, Kanter K, Ohye R, Bacha EA, Tweddell J, Schwartz SM, Minich LL, et al. The Pediatric Heart Network residual lesion score study: design and objectives. *J Thorac Cardiovasc Surg*. 2020;160:218–223.e211. doi: 10.1016/j.jtcvs.2019.10.146
14. Chen Y, Lawrence J, Stockbridge N. Days alive out of hospital in heart failure: insights from the PARADIGM-HF and CHARM trials. *Am Heart J*. 2021;241:108–119. doi: 10.1016/j.ahj.2021.03.016
15. Jerath A, Austin PC, Wijeysundera DN. Days alive and out of hospital: validation of a patient-centered outcome for perioperative medicine. *Anesthesiology*. 2019;131:84–93. doi: 10.1097/ALN.0000000000002701
16. White HD, O'Brien SM, Alexander KP, Boden WE, Bangalore S, Li J, Manjunath CN, Lopez-Sendon JL, Peteiro J, Gosselin G, et al. Comparison of days alive out of hospital with initial invasive vs conservative management: a prespecified analysis of the ISCHEMIA trial. *JAMA Cardiol*. 2021;6:1023–1031. doi: 10.1001/jamacardio.2021.1651

17. Agus MSD, Wypij D, Hirshberg EL, Srinivasan V, Faustino EV, Luckett PM, Alexander JL, Asaro LA, Curley MAQ, Steil GM, et al. Tight glycemic control in critically ill children. *N Engl J Med*. 2017;376:729–741. doi: 10.1056/NEJMoa1612348
18. Yehya N, Wong HR. Adaptation of a biomarker-based sepsis mortality risk stratification tool for pediatric acute respiratory distress syndrome. *Crit Care Med*. 2018;46:e9–e16. doi: 10.1097/CCM.0000000000002754
19. Yehya N, Keim G, Thomas NJ. Subtypes of pediatric acute respiratory distress syndrome have different predictors of mortality. *Intensive Care Med*. 2018;44:1230–1239. doi: 10.1007/s00134-018-5286-6
20. Whitney JE, Feng R, Koterba N, Chen F, Bush J, Graham K, Lacey SF, Melenhorst JJ, Parikh SM, Weiss SL, et al. Endothelial biomarkers are associated with indirect lung injury in sepsis-associated pediatric acute respiratory distress syndrome. *Crit Care Explor*. 2020;2:e0295. doi: 10.1097/CCE.0000000000000295
21. Baker-Smith CM, Wilhelm CM, Neish SR, Klitzner TS, Beekman RH III, Kugler JD, Martin GR, Lannon C, Jenkins KJ, Rosenthal GL, et al. Predictors of prolonged length of intensive care unit stay after stage I palliation: a report from the National Pediatric Cardiology Quality Improvement Collaborative. *Pediatr Cardiol*. 2014;35:431–440. doi: 10.1007/s00246-013-0797-y
22. Mori M, McCracken C, Maher K, Kogon B, Mahle W, Kanter K, Alsoufi B. Outcomes of neonates requiring prolonged stay in the intensive care unit after surgical repair of congenital heart disease. *J Thorac Cardiovasc Surg*. 2016;152:720–727.e721. doi: 10.1016/j.jtcvs.2016.04.040
23. Saharan S, Legg AT, Armsby LB, Zubair MM, Reed RD, Langley SM. Causes of readmission after operation for congenital heart disease. *Ann Thorac Surg*. 2014;98:1667–1673. doi: 10.1016/j.athoracsur.2014.05.043
24. Smith AH, Doyle TP, Mettler BA, Bichell DP, Gay JC. Identifying predictors of hospital readmission following congenital heart surgery through analysis of a multiinstitutional administrative database. *Congenit Heart Dis*. 2015;10:142–152. doi: 10.1111/chd.12209
25. Hanke SP, Joy B, Riddle E, Ravishankar C, Peterson LE, King E, Mangeot C, Brown DW, Schoettker P, Anderson JB, et al. Risk factors for unanticipated readmissions during the interstage: a report from the National Pediatric Cardiology Quality Improvement Collaborative. *Semin Thorac Cardiovasc Surg*. 2016;28:803–814. doi: 10.1053/j.semtcvs.2016.08.011
26. Gardner MM, Mercer-Rosa L, Faerber J, DiLorenzo MP, Bates KE, Stagg A, Natarajan SS, Szwast A, Fuller S, Mascio CE, et al. Association of a home monitoring program with interstage and stage 2 outcomes. *J Am Heart Assoc*. 2019;8:e010783. doi: 10.1161/JAHA.118.010783
27. STS congenital heart surgery database. 2021.
28. Jacobs JP. The Society of Thoracic Surgeons congenital heart surgery database public reporting initiative. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2017;20:43–48. doi: 10.1053/j.pcsu.2016.09.008
29. Pediatric Cardiac Critical Care Consortium (PC4). 2021.
30. Vinocur JM, Moller JH, Kochilas LK. Putting the pediatric cardiac care consortium in context: evaluation of scope and case mix compared with other reported surgical datasets. *Circ Cardiovasc Qual Outcomes*. 2012;5:577–579. doi: 10.1161/CIRCOUTCOMES.111.964841
31. Gaies M, Donohue JE, Willis GM, Kennedy AT, Butcher J, Scheurer MA, Alten JA, William Gaynor J, Schuette JJ, Cooper DS, et al. Data integrity of the Pediatric Cardiac Critical Care Consortium (PC4) clinical registry. *Cardiol Young*. 2016;26:1090–1096. doi: 10.1017/S1047951115001833
32. Gaies MG, Jeffries HE, Niebler RA, Pasquali SK, Donohue JE, Yu S, Gall C, Rice TB, Thiagarajan RR. Vasoactive-inotropic score is associated with outcome after infant cardiac surgery: an analysis from the Pediatric Cardiac Critical Care Consortium and Virtual PICU System Registries. *Pediatr Crit Care Med*. 2014;15:529–537. doi: 10.1097/PCC.0000000000000153
33. Costello JM, Mongé MC, Hill KD, Kim S, Pasquali SK, Yerokun BA, Jacobs JP, Backer CL, Mazwi ML, Jacobs ML, et al. Associations between unplanned cardiac reinterventions and outcomes after pediatric cardiac operations. *Ann Thorac Surg*. 2018;105:1255–1263. doi: 10.1016/j.athoracsur.2017.10.050
34. Dorobantu DM, Ridout D, Brown KL, Rodrigues W, Sharabiani MTA, Pagel C, Anderson D, Wellman P, McLean A, Cassidy J, et al. Factors associated with unplanned reinterventions and their relation to early mortality after pediatric cardiac surgery. *J Thorac Cardiovasc Surg*. 2021;161:1155–1166.e1159. doi: 10.1016/j.jtcvs.2020.10.145
35. Gaies M, Tabbutt S, Schwartz SM, Bird GL, Alten JA, Shekerdemian LS, Klugman D, Thiagarajan RR, Gaynor JW, Jacobs JP, et al. Clinical epidemiology of extubation failure in the pediatric cardiac ICU: a report from the Pediatric Cardiac Critical Care Consortium. *Pediatr Crit Care Med*. 2015;16:837. doi: 10.1097/PCC.0000000000000498
36. Benneyworth BD, Mastropietro CW, Graham EM, Klugman D, Costello JM, Zhang W, Gaies M. Variation in extubation failure rates after neonatal congenital heart surgery across Pediatric Cardiac Critical Care Consortium hospitals. *J Thorac Cardiovasc Surg*. 2017;153:1519–1526. doi: 10.1016/j.jtcvs.2016.12.042
37. Pollack MM, Holubkov R, Funai T, Clark A, Berger JT, Meert K, Newth CJL, Shanley T, Moler F, Carcillo J, et al. Pediatric intensive care outcomes: development of new morbidities during pediatric critical care. *Pediatr Crit Care Med*. 2014;15:821–827. doi: 10.1097/PCC.0000000000000250
38. Parra DA, Totapally BR, Zahn E, Jacobs J, Aldousany A, Burke RP, Chang AC. Outcome of cardiopulmonary resuscitation in a pediatric cardiac intensive care unit. *Crit Care Med*. 2000;28:3296–3300. doi: 10.1097/00003246-200009000-00030
39. Elsharkawy HA, Li L, Esa WAS, Sessler DI, Bashour CA. Outcome in patients who require venoarterial extracorporeal membrane oxygenation support after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2010;24:946–951. doi: 10.1053/j.jvca.2010.03.020
40. Baslaim G, Bashore J, Al-Malki F, Jamjoom A. Can the outcome of pediatric extracorporeal membrane oxygenation after cardiac surgery be predicted? *Ann Thorac Cardiovasc Surg*. 2006;12:21.
41. Naim MY, Gaynor JW, Chen J, Nicolson SC, Fuller S, Spray TL, Dlugos DJ, Clancy RR, Costa LV, Licht DJ, et al. Subclinical seizures identified by postoperative electroencephalographic monitoring are common after neonatal cardiac surgery. *J Thorac Cardiovasc Surg*. 2015;150:169–178; discussion 178–180. doi: 10.1016/j.jtcvs.2015.03.045

SUPPLEMENTAL MATERIAL

Table S1: Categorization of 30-day, 6-month and 12-month mortalities (n=88)

	30-day (n = 37)		31 days to 6 months (n = 43)		6 to 12 months (n = 8)	
	Composite n=37	No composite	Composite n=31	No composite n=12	Composite n=4	No composite n=4
Cardiac arrest	9	-	12	7	0	0
Cardiogenic shock & MSOF	21	-	14	4	4	2
Respiratory failure	0	-	1	1	0	0
Neurologic failure	5	-	2	0	0	0
Other	2	-	2	0	0	2

Abbreviations: MSOF = multi-system organ failure

Table S2: Categorization of CICU prolonged ICU LOS ≥ 30 days (n = 110)

Delayed sternal closure	73 (66.4%)
RRT	4 (3.6%)
ECMO	43 (39.1%)
CPR	10 (9.1%)
Seizures	32 (29.1%)

Results presented as n (%).
Abbreviations: RRT = renal replacement therapy, ECMO = extracorporeal membrane oxygenation, CPR = cardiopulmonary resuscitation.

Table S3: Categorization of CICU Readmissions (n=85)

CICU readmission in same admission	75 (88.2%)
CICU readmission after hospital discharge	10 (11.8%)
Recovery after unplanned cardiac operation/procedure	20 (23.5%)
Recovery after unplanned cardiac catheterization	14 (16.5%)
Cardiac arrest	3 (3.5%)
Cardiorespiratory-medical	40 (47.1%)
Non-cardiac-medical	8 (9.4%)

Results presented as n (%).
Abbreviations: CICU = cardiac intensive care unit

Table S4: Test characteristics of ICU-30 Outcome with 12-month mortality

AUROC (95% CI)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
0.81 (0.77-0.85)	81.8%	80.0%.	31.0%	97.65%