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

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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
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 |

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 multi-system 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,6,9 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; 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**                        |                      |                        |                               |         |
| Female                         | 354 (39.9%)          | 95 (40.9%)             | 259 (39.5%)                   | 0.707   |
| Male                           | 533 (60.1%)          | 137 (59.1%)            | 396 (60.5%)                   |         |
| **Race**                       |                      |                        |                               |         |
| White                          | 522 (59.9%)          | 123 (63.0%)            | 399 (60.9%)                   | 0.224   |
| 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**                  |                      |                        |                               |         |
| 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 (60.4%)            | 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 (8.9, 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

| Outcome                        | Total   | AUROC   | 95% CI    |
|--------------------------------|---------|---------|-----------|
| Prolonged CICU LOS (≥30 d)     | 110 (12.5%) | 0.81   | 0.77–0.85 |
| Mortality within 30-d          | 37 (4.2%)    | 0.81   | 0.77–0.85 |
| CICU readmission               | 85 (9.6%)    | 0.81   | 0.77–0.85 |
| Composite outcome              | 232 (26.2%)  | 0.81   | 0.77–0.85 |

Results presented as n (%). ICU-30 outcome is categorized 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.

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

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

**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 categorized as either 30-day mortality, prolonged ICU LOS ≥30 days, or CICU readmission within 30 days.

**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 categorized 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

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Supplemental Material

Tables S1–S4

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### 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)

| Condition                  | Count (Percentage) |
|----------------------------|--------------------|
| 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)

| Category                                      | Count | Percentage |
|-----------------------------------------------|-------|------------|
| 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%                    |