Reviewer’s report

Title: One Size Does Not Fit All: The Influence of Age at Surgery on Outcomes following Norwood Operation

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Reviewer: Robert D B Jaquiss

Reviewer’s report:

The manuscript entitled “One Size Does Not Fit All: The Influence of Age at Surgery on Outcomes Following Norwood Operation” has been revised to address the suggestions and concerns of two reviewers, and resubmitted. The conclusions of the revised manuscript remain unaltered from the original submission:
• For the cohort of children (n=105) undergoing the Norwood operation at Seattle Children’s Hospital from 2004 to 2011, survival at 30 days post-Norwood (86%) was worse among the group (n=43) who were younger than 7 days at Norwood operation than survival at 30 days post-Norwood (97%) among the group (n=65) who were older than 7 days at Norwood, p=0.04 for the difference in survival at 30 days.
• Among those who survived to hospital discharge after Norwood (n=91), late death occurred at a higher rate among those who were less than 7 days at the time of Norwood, (25% vs. 5%, p<0.005)

The revisions in the manuscript address the suggestions of the reviewers nearly completely:
• Elimination of some language in the introduction
• Explicit statement that there was no statistical evidence of an era effect (“year of surgery” was not a risk factor for mortality in univariable analysis), accompanied by a statement in the limitations section that “…results clearly improved over time indicating that era may have been an important factor.”
• Inclusion of a reference which described lower systemic oxygen delivery among younger (<8 days) patients undergoing Norwood operation

The revised manuscript did not include the correction of a typographical error in the methods section of the abstract – currently says “/>= 30 days” and should say “</= 30 days”.

Because the authors have addressed the comments and suggestions of the reviewers (except for the trivial typographical error), I cannot in good conscience oppose publication. However, having read the manuscript carefully yet again, I cannot support its publication either, for the following reasons:
• The central message of the paper is that young age is a risk factor for (early and late) death after Norwood operation, and yet…
Survival is assessed at discrete time points, rather than by a much more meaningful Kaplan-Meier/log rank assessment. I am skeptical that KM/LR comparison would identify a difference survival between the groups.

In a single paragraph (page 7, Patient Outcomes), the authors assess early survival in three different ways:

- “Operative mortality was 8% (n=8)……”
- “In-hospital mortality was 11% (n=12)…. ”
- “Using the STS definition for operative mortality… 14 (13%) deaths…”

If the authors used only the third of the definitions (STS), the now-standard and preferred approach, then early death WAS NOT statistically significantly less likely among older patients (10% vs. 19%, p=0.18). This significantly complicates the remainder of the work.

The flow chart (Figure 1) is incomplete in that not all patients are accounted for; specific “end states” are given for only 35 patients (12 in hospital deaths post-Norwood, 2 in hospital deaths post-Norwood-post-transplant, 6 interstage transplants, 5 interstage deaths, 1 transplanted post BDG, and 9 post BDG waiting for Fontan). Seventy patients are unaccounted for. This diagram needs to be re-drawn (I assume that one or several of the numbers are simply typographical errors).

Figure 2 portrays “operative mortality” using the 30 day definition. Since this is NOT the currently accepted (STS) definition of operative mortality, the authors should perhaps use “30 day mortality” instead.

Figure 3 shows “any state death post discharge”, which is fairly hard to interpret, and as stated previously far less useful than a simple survival curve with numbers at risk at each interval included. How would a post transplant death be classified? Would this be different depending on when the transplant occurred?

The authors use survival (at some time point) as their outcome measure. It would surely be more reasonable to use “transplant-free” survival. They transplanted 8 patients of the original cohort, all of whom would presumably have died otherwise (and two of whom died anyway). The use of the more meaningful endpoint – transplant free survival – would seem much more sound physiologically. This has been fairly standard (SVR trial for example) for quite some time. If this would not change the analysis, the authors should say so.

I am still skeptical that there is not a profound era effect, and am not convinced by the statement that “year of surgery” was not a risk factor on multivariable modeling. To be fair, neither was age. The authors chose to discretize age (dichotomization) to perform their analysis, but assess era by using a continuous variable. Why is discretization valid for age but not era? One could imagine dichotomizing era by mid-point of study or by first 52 vs. second 52 patients for example.

The authors assess post-discharge mortality, but do not describe post-discharge management. Did they use a home-surveillance protocol
throughout the period of study? At all? Or beginning mid-study? There seems to be consensus (if not proof) that such protocols improve interstage survival, and if the authors initiated such a protocol mid-study period, or selectively to remote or local patients, this might bias outcomes.

• The authors are now at different institutions with different referral patterns and, potentially, different care protocols. If they believe, as the title of their work suggests, that there is intrinsic biologic risk attached to the Norwood procedures done in patients younger than seven days, how has this informed their practice at their new institutions?

In conclusion, the authors have met the requirement for revision proposed by my fellow reviewer and me, and so I could not oppose publication of the work. That said, I remain deeply skeptical of the study and its conclusions.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I have no competing interests.