Reviewer's report

Title: Reduced Dicer expression in the cord blood of infants admitted with severe respiratory syncytial virus disease

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Reviewer: Massimiliano Fabbiani

Reviewer's report:

In this manuscript Inchley et al. investigate the association between the degree of Dicer expression in cord blood collected at birth and the development of RSV disease in the first year of life. The main finding is a downregulation of Dicer expression in patients with severe disease in comparison to those not developing RSV infection. No significant downregulation was observed in the mild disease group. These results could suggest that reduced Dicer expression can be linked to RSV disease development and severity.

Results are interesting and the manuscript is well written. However some issues regarding study design and its limitations need to be addressed before acceptance.

Note for the editor: since I’m not a clinician, my evaluation of laboratory methods could be inaccurate. These could be reviewed by another referee at the discretion of the editor.

MAJOR COMPULSORY REVISIONS

1. Page 6, Patient identification and clinical information:
   a. please define what you means with the term healthy controls: I suppose that they are children not hospitalized for RSV infection in the first year of life and not tested or tested negative in primary care.
   b. Why only 17 healthy controls were selected from this large cohort? A larger number could have improved the statistical power of the analysis.
   c. How did you confirm that controls were not admitted for treatment at other pediatric units?

2. Page 7, Disease definition and classification: the inclusion as cases of a number of patients “tested for RSV by their primary care physicians, but not referred for admission” introduces a potential bias. Criteria applied by primary care physicians for RSV testing could be very variable and routine test for RSV in all patients with suspected viral respiratory infection at a primary care level is not probable. How can you be sure that other infants with similar respiratory disease severity were not tested for RSV by primary care physician and consequently selected as healthy controls? This could also explain the reason why you did not find any difference in Dicer expression between controls and mild disease group.
This limitation should be recognized and adequately discussed in the discussion section.

3. Table 2:
   a. Data from 51 infants with RSV infection are reported. However, only 37 were analyzed for Dicer expression. As a consequence, only data of these 37 enrolled patients should be presented in table.
   b. Age on admission: is it described as mean (SD)? Otherwise the interquartile range should be specified in parenthesis.
   c. To facilitate data interpretation, categorical variables should be described as n (%) and not as the absolute number only.
   d. The authors state in the note that no significant between-groups differences were observed. However, a column showing the exact p value for each variable comparison should be added. Also a statistical trend can be of some value when comparing groups with a low number of patients.

4. Table 3:
   a. Data from 51 infants with RSV infection are reported. However, only 37 were analyzed for Dicer expression. As a consequence, only data of these 37 enrolled patients should be presented in table.
   b. The total number of patients with mild and severe disease should be added.
   c. To facilitate data interpretation, categorical variables should be described as n (%) and not as the absolute number only.
   d. The exact p value (and not “n/s”) for each variable comparison should be showed. Also a statistical trend can be of some value when comparing groups with a low number of patients.
   e. What do you mean with the term “primary or secondary diagnosis”?

5. Table 4:
   a. The number of controls should be specified in the title.
   b. The number of patients with mild or severe disease should be specified in the title or in the table.
   c. The exact p value (and not “n/s”) should be showed. Also a statistical trend can be of some value when comparing groups with a low number of patients.
   d. You showed that, when compared to control subjects, severe disease group demonstrated significant Dicer downregulation but mild disease group did not. But is there significant difference in Dicer expression between severe and mild disease group? This could be stated in results section and discussed.

6. Some other limitations, in addition to those highlighted in the points above, should be recognized and discussed:
   a. The retrospective selection of infants could have introduced some biases (some patients not tested for RSV despite respiratory infection, inaccurate compilation of medical charts…).
   b. The low number of patients and controls included could have limited the
statistical power of the analysis.

MINOR ESSENTIAL REVISIONS
1. Abstract: a brief mention on criteria used for the control group (subject not infected by RSV) selection should be provided. In particular, it should be specified that Dicer expression in severe and mild disease groups was compared to RSV uninfected infants.
2. Page 12, Results: in the last line, did you mean that there were no clinical differences between the 37 patients included and the 14 excluded by qPCR experiment? Please specify “data not shown” (these data are not shown in tables).

DISCRETIONARY REVISIONS
1. Introduction, page 4: correct the sentence “although research the last 10 years has provided important clues” to “although research has provided important clues in the last 10 years”.
2. Page 6, identification of RSV infection: correct the sentence “If negative, the NPA was for RSV analyzed by multiplex RT-PCR” to “If negative, the NPA was analyzed for RSV by multiplex RT-PCR”.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests