PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluation of unmodifiable and potentially modifiable factors affecting peripheral intravenous device related complications in neonates: a retrospective observational study.
AUTHORS	van Rens, Matheus F.P.T.; Hugill, Kevin; Mahmah, Mohamad A.; Bayoumi, Mohammad; Francia, Airene L.V.; Garcia, Krisha L.P.; van Loon, F.H.J.;

VERSION 1 – REVIEW

REVIEWER	Keogh, Samantha Queensland University of Technology, School of Nursing
REVIEW RETURNED	13-Feb-2021

GENERAL COMMENTS	Thank you for giving me the opportunity to review this paper. The neonatal community is a vulnerable and high user population that need to have their vascular access preserved and cared for. The authors are to be commended on collation and analysis of such a large cohort. I have some queries though, largely related to type of statistical analysis chosen. I hope the authors take the time to address this. BMJ Open NICU study Abstract" Setting. Given large sample size, was this single site or multi site study? Results. (comments will apply to main results also) the SD fro the mean dwell times is large. ? a typo in one off reported SDs. Would median and IQR be better reported here? What statistical test performed against risk factors? Page 7: What is role/prevalence of umbilical vascular access? Statistical analysis: Intrigued as to why researchers used logistic regression fro a time based variable. Usually Cox' Hazard Regression is used to look at risk of failure (or success) with a reference point. Can Researchers justify why logistic regression used and how (device dwell) time was factored in? For difference between continuous variables, ideally rate/device days, usually use survival analysis and log rank test. Results: Interesting disparity between number of cannulations and number of attempts. Is first insertion success also an issue in this population? Vessel preservation ever important especially in such a young and vulnerable patient. Also, following on from statistical test query. It doesn't necessary carry that the lowest incidence of a complication carries the lowest

	risk. It is relative to time (i.e. a rate per device days rather raw proportion) and compared to a referent point. What was the criteria for application of IV Watch(R)? Sensitivity and Specificity reported is poor. A dedicated study would be needed to demonstrate this I.e. comparison of IV Watch sensitivity/specificity compared to a 'gold standard'. Discussion: Good points about how this study has added to body of knowledge on use of touch-look-compare and PIVIE assessment tools. As authors stated, need consensus on this in practice and research. Conclusion Feel like conclusion weak and not practice given size and significance of study. There is real opportunity to use appropriate collated and analysed risk factor data to inform practice. For e.g., the risk factors identified as significantly could potentially inform a model that could be used to detect NNT/NNH for PIVC failure or PIVIE.

REVIEWER	Travan, Laura University of Trieste
REVIEW RETURNED	27-Feb-2021

GENERAL COMMENTS	Abstract Page 3: Line 26. NICU…where? Please specify Line 31. Use the acronym "PIVC" never explained before (you wrote "peripheral intravenous access" and not "catheter" in line 13…) Design and setting Page 8 Line 16. The outcome of interest… the outcome of the study is… Participants and sample size Page 9 Line 14. You wrote…"saphenous and elbow veins generally avoided". It would be interesting and didactic to explain why. Line 38. What about your Hospital protocol on the total dwell time of PIVC after insertion? Two, three weeks? You don't mention anything pain procedure control. Please add. Results Page 12 Line 18. Mean duration of gestation 34+6…= mean gestational age. Please specify min and max or SD. The gestational age

	seems rather high – and also the mean birth weight – for the need of PIVC insertion: would you argue about this item in the discussion? Do you have a relevant number of surgical patients or a high incidence of late onset sepsis? Discussion Page 15. Line 23. You state that …"the risk for complication was increased in participants (newborns?subjects?) with a lower weight at birth…"Ozkiraz S in 2013 (J Vasc Access) published different results. You could discuss about this item. Page 17 Line 20. Preferred cannulation side dorsal hand…? Are you sure there are not papers in literature stating viceversa? Please check.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
3. Prof. Samantha Keogh, Queensland University of Technology, Queensland University of Technology. Comments to the Author: Thank you for giving me the opportunity to review this paper. The neonatal community is a vulnerable and high user population that need to have their vascular access preserved and cared for. The authors are to be commended on collation and analysis of such a large cohort. I have some queries though, largely related to type of statistical analysis chosen. I hope the authors take the time to address this.
• We thank the reviewer for the compliments and the chance to revise the manuscript according to these valuable suggestions.

4. Abstract: Setting. Given large sample size, was this single site or multisite study? Results. (comments will apply to main results also) the SD from the mean dwell times is large. ? a typo in one off reported SDs. Would median and IQR be better reported here? What statistical test performed against risk factors?
• This study was a single site study, performed in a large medical center. We added this information to the abstract of the manuscript. The represented SD in the results statement of the abstract was an inaccurate typo. We checked all our calculations and statistics; the correct mean dwell time and SD must be 31 ±23. This is revised and presented correctly in the abstract of the manuscript. Risk factors we calculated with Cox' Hazard Regression analysis and represented with odds ratios, which corresponds to the outcomes as represented in the results section.

5. Methods: What is role/prevalence of umbilical vascular access?
• According to hospital policy, umbilical vascular access devices are used for short term treatment. When further (long term) treatment is indicated, a vascular access device will be inserted in a peripheral or central venous. With the current study focusing on peripheral intravenous access devices, no data was collected or analyzed for central venous or umbilical access devices.

6. Statistical analysis: Intrigued as to why researchers used logistic regression from a time-based variable. Usually Cox' Hazard Regression is used to look at risk of failure (or success) with a reference

point. Can Researchers justify why logistic regression used and how (device dwell) time was factored in? For difference between continuous variables, ideally rate/device days, usually use survival analysis and log rank test.
• According to the reviewer's suggestion, we checked the statistical analyses and revised in rigorously. Stepwise Cox' hazard regression analyses were used to provide correlations between variables regarding the outcome of this study and obtain its odds ratio with 95% confidence interval. Items with a significant relationship ($P<0.01$) to the outcome of this study from a univariate analysis were entered in these analyses. The stepwise method was utilized to remove independent variables that did not make a significant contribution to the primary outcome variable using a backward elimination process based on the Wald statistic and level of significance, with the removal criteria set at $P=0.01$, to obtain a model with a minimal set of variables. Besides, as mentioned in the statistical analyses section, differences between survival time of the intravenous catheter according to its reason for premature removal were represented with Mantel-Cox $\chi 2$. These analyses, regarding dwell-times of the intravenous access devices, were also used for comparisons of the other outcome measurements.

7. Results: Interesting disparity between number of cannulations and number of attempts. Is first insertion success also an issue in this population? Vessel preservation ever important especially in such a young and vulnerable patient.
• We fully agree with the reviewer. First attempt cannulation success is an important issue during intravenous cannulation, especially in neonates. As shown in Table 1, cannulation was successful on the first attempt in 8481 patients, but 4497 suffered from a failed first attempt (35%). The implementation of the 5Rs rule, as described in the introduction section, was recently introduced into the department and followed in a proactive way. Despite, up to now, no results are available about this implementation.

8. Results: Also, following on from statistical test query. It doesn't necessary carry that the lowest incidence of a complication carries the lowest risk. It is relative to time (i.e., a rate per device days rather raw proportion) and compared to a referent point.
• The reviewer raises an interesting point here. As made visible in Figure 1, 50% of intravenous access devices were removed within the first 38 hours and differed regarding the reason for removal. In general, the time-point of 38 hours can be seen as a cut-off point. Subsequently, the overall intravenous catheter complication rate was 18 per 1000 catheter days.

9. Results: What was the criteria for application of IV Watch(R)? Sensitivity and Specificity reported is poor. A dedicated study would be needed to demonstrate this I.e., comparison of IV Watch sensitivity/specificity compared to a 'gold standard'.
• As mentioned in the methods section, The ivWatch® was introduced into use in January 2020 after a small pilot evaluation study and applied since then with infants weighing more than 1000 grams (page 6, Measurements and data collection).
• Pilot study: van Rens M, Hugill K, Francia AV. A new approach for early recognition of peripheral intravenous (PIV) infiltration: a pilot appraisal of a sensor technology in a neonatal population. Vascular Access. 2019;5(2):38-41. doi:10.33235/va.5.2.38-41

10. Discussion: Good points about how this study has added to body of knowledge on use of touch-look-compare and PIVIE assessment tools. As authors stated, need consensus on this in practice and research.
• We thank the reviewer for this complement.

11. Conclusion: Feel like conclusion weak and not practice given size and significance of study. There is real opportunity to use appropriate collated and analyzed risk factor data to inform practice. For e.g., the risk factors identified as significantly could potentially inform a model that could be used to detect NNT/NNH for PIVC failure or PIVIE.
• We rephrased the conclusion of our manuscript, in agreement with your suggestions. We therefore added “Most infants experienced a vascular access related complication” to the conclusion section. Furthermore, with PIVIE being the most important complication in the neonatal population, we represented the relative risk for the occurrence of PIVIE in the conclusion section as follows: “the most frequently observed complication in the neonatal population is a PIVIE, with a RR of 3.14 (3.04 to 3.25)”. We believe this makes the conclusion more useful in clinical practice.

Reviewer: 2

12. Dr. Laura Travan, University of Trieste. Comments to the Author: The paper has a large sample size and is really "honest". I think it is important to publish also this kind of paper.
• We thank the reviewer for the valuable assessment and the compliments given. We revised the manuscript accordingly.

13. Abstract: NICU…where? Please specify
• We have added the full description of the abbreviation and included details about the location of the study setting to the abstract section.

14. Abstract: Use the acronym “PIVC” never explained before (you wrote “peripheral intravenous access” and not “catheter” in line 13…)
• We removed the abbreviation “PIVC” from the abstract and replaced it by its full description.

15. Design and setting: The outcome of interest… the outcome of the study is…
• This has been revised accordingly. Furthermore, on page 6 (Measurements and data collection) we added: “the main outcome was the occurrence of any peripheral intravenous cannulation failure, leading to unplanned removal of the device before completion of the intended intravenous therapy”.

16. Participants and sample size: You wrote…”saphenous and elbow veins generally avoided”. It would be interesting and didactic to explain why.
• We added to the manuscript (page 5, Procedure): “Proactive choices to prevent patients from running out of veins and being labeled as a difficult vascular access patient are key in the selection of cannulation site and intravenous catheter. For that reason, saphenous and elbow veins generally are avoided for cannulation”.

17. Participants and sample size: What about your Hospital protocol on the total dwell time of PIVC after insertion? Two, three weeks?
• The reviewer raised an interesting point here. We added on page 6 (Procedure): “According to hospital protocols, and based on international guidelines, there is no evidence for routine rotation of vascular access devices in the neonatal population”.

18. Results: Mean duration of gestation 34+6…= mean gestational age. Please specify min and max or SD. The gestational age seems rather high – and also the mean birth weight – for the need of PIVC insertion: would you argue about this item in the discussion? Do you have a relevant number of surgical patients or a high incidence of late onset sepsis?

• According to the reviewer's suggestions, we revised to the presentation of mean gestational age into 34+6 (23 to 43) weeks. We added the lowest and highest value between brackets. No surgical patients were included in this population, nor did we have a high incidence of late onset sepsis. It seems more like a coincidence, possibly due to the large sample size without restriction to demographic and baseline characteristics.

19. Discussion: You state that …"the risk for complication was increased in participants (newborns, subjects) with a lower weight at birth…"Ozkiraz S in 2013 (J Vasc Access) published different results. You could discuss about this item.
• It seems clear that consensus was not reached about factors affecting the risk for complication regarding vascular access devices. However, the published study the reviewer referred to, seems to be about PICC insertions in a comparable context. Nonetheless, the risk for complications, as well as the type of complications and its outcomes are totally different when compared to those for peripheral intravenous catheter insertion, which was the subject of this study.

20. Discussion: Preferred cannulation side dorsal hand…? Are you sure there are not papers in literature stating vice versa? Please check.
• It is interesting to see other publications, which we have of course studied before writing the manuscript. The dorsum of the hand being the preferred cannulation site in our study is a result of preference in our clinic. It is debatable which cannulation site is most optimal in the neonatal population, which could be an interesting question for further (literature) research.

VERSION 2 – REVIEW

REVIEWER	Keogh, Samantha Queensland University of Technology, School of Nursing
REVIEW RETURNED	31-May-2021

GENERAL COMMENTS	Dear Authors. Thank you for taking the time to revise the manuscript. Normal practice is a table of response to reviewers acknowledging and detailing responses to these in addition to tracked change manuscript. I note the addition of stated Cox Hazard Regression, however you continue to report results as a RIsk Ratio or Odds ration when in fact it is a Hazard Ratio (HR). Please check and amend this and engage statistical advice if necessary. This is an important cohort study so it is important to be accurate and complete with reporting.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Prof. Samantha Keogh, Queensland University of Technology, Queensland University of Technology

We thank the reviewer for the accurate review of our manuscript. Actually, we reported Hazard Ratio's throughout the study, but mentioned them incorrect as Odds Ratio's. Therefore, after checking the entire

data analyses with our statistician, we changed the reported manuscript accordingly in the abstract and results section. We fully agree with the reviewer this is an important cohort study, so we felt the need to check the complete manuscript.