

Peer Review File

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Reviewer A#

Comment 1: Huang et al undertook a retrospective population-based study in Northern China and included 568 extremely preterm infants. The authors utilised a training dataset to identify a predictive model for mortality. Seven risk factors were included in the model, which had an area under the ROC curve of 0.886 for the validation set in predicting in-hospital mortality. The positive predictive value was 0.383 for the training dataset and 0.288 for the validation dataset. This is an interesting topic and the authors included a large number of infants for which they should be commended.

Reply 1: We thank the reviewer for a positive appraisal of our manuscript.

Comment 2: One hospital was included which admitted only transferred neonates (no inborn, I presume as no maternity unit) – did this affect your results given that in-born was a variable in the prediction model and thus all infants included from this hospital would be out-born.

Reply 2: Thank you for your comment. The hospital with no maternity unit treated a total of 15 EPIs included in our study, of which 4 died. Compared with the other hospitals (71 deaths out of 553 cases), there was no statistically significant difference in mortality ($P=0.352$).

Comment 3: It is interesting that you excluded a large proportion of infants (234 infants out of the total 803) of whom parents chose to give up life sustaining treatment. I wonder if those infants had a worse prognosis and thus these might affect results differently if included. Could you include these infants/do a sub-analysis for them?

Reply 3: Thank you for the constructive suggestions. Due to the limitations of a retrospective study, we were unable to accurately identify the reasons for discontinuing treatment (whether

it is poor prognosis or economic reasons) and the survival rate of the EPIs receiving incomplete care.

Among the 234 EPIs receiving incomplete care, those who were discharged with unstable vital signs (requiring invasive/noninvasive mechanical ventilation, inotropic drugs infusion, or lack of adequate feeding) were predicted to die, while those with relatively stable vital signs were predicted to have indefinite outcomes. It was worth noting that a significant proportion (43.2%) of preterm infants with treatment abandoned were discharged from the hospital with relatively stable vital signs and a chance of survival.

Therefore, we cannot accurately assess the impact of incomplete treatment on this prediction model, so the analysis of the predictive model was only conducted in EPIs who received complete care from birth to discharge. We hope that through our efforts, the proportion of infants receiving incomplete care would gradually decrease in the future studies.

Changes in the text: We added some data (see Page 7, line 182 to Page 8, line 195; eTable 1 and eTable 2 in the supplement) to describe the details of this subgroup. The results showed that the EPIs who received incomplete care (treatment abandoned by the parents before discharge) had a lower percentage of ANS, lower 5-min Apgar score, and higher percentage of invasive MV and pulmonary hemorrhage (all $P < 0.05$, eTable 1 in the Supplement). Comparing the clinical characteristics of EPIs who died at different time points (<7 days vs. ≥ 7 days) and in different groups (complete care group vs. incomplete care group), the EPIs who died at <7 days in the complete care group had a higher incidence of pulmonary hemorrhage (48.3% vs. 28.9%, $P < 0.05$), whereas among those who died at ≥ 7 days, the incomplete care group had a higher incidence of severe IVH or PVL (53.7% vs. 23.5%, $P < 0.05$, eTable 2 in the Supplement).

Comment 4: The outcomes you included were death, discharge and transfer. Would you be able to provide more information about infants who were transferred – did these infants survive discharge from hospital for example?

Reply 4: Unfortunately, due to the limitations of a retrospective study, this subgroup was not followed up. A total of 28 EPIs were referred in this study, mostly for further surgical treatment (NEC surgery or ROP intervention). Before referral, their length of hospital stay was 49.0 (11.5, 66.3) days.

Comment 5: I think there is an error in the methods when described PVL diagnosis by echocardiography – do you mean by cranial ultrasonography?

Reply 5: We are extremely grateful to the reviewer for pointing out this problem. We have revised this error.

Changes in the text: We have modified our text as advised (see Page 5, line 125).

Comment 6: What is the end point of the variable chosen – is this any of the diagnoses up until the point of discharge/death? Clearly the closer to discharge the variables occurred then the better the model, however this is less useful in providing early prediction.

Reply 6: The endpoint of the study was the occurrence of the primary outcome (discharge or death). The median time to death was 2.0 (0.9, 5.0) days; 77.3% of deaths happened within 7 days of birth, of which 25.3%, 28.0%, and 24.0% infants died at <24 h, 1–<3 days, and 3–<7 days, respectively, whereas 22.7% died at ≥ 7 days of birth. The seven variables included in the study also typically appeared early in the management of preterm infants; therefore, we believe the results might help clinicians identify EPIs with the risk of poor prognosis early.

Changes in the text: We have modified our text to make this clearer (see Page 7, line 172–174).

Comment 7: Did infants with shock receive inotropic support? I suspect use of inotropes may affect the outcomes, however, cannot see any data regarding this.

Reply 7: Shock was defined in this study as inadequate oxygen supply to vital organs resulting from circulatory failure that manifested as hypotension, oliguria, acidosis, and prolonged capillary refill time. Interventions that were used to treat shock in the hospitals included in this study encompassed isotonic fluid boluses, blood transfusion, inotropes (e.g., dopamine, dobutamine, epinephrine), and corticosteroids (e.g., hydrocortisone).

However, some hospitals included routine administration of low-dose inotropic therapy (usually dopamine) for empirical treatment of EPIs on high-frequency ventilators or with low blood pressure (BP) to maintain stable BP. Therefore, this information was not collected in this study. However, this is a very good suggestion that we will consider carefully in the subsequent

studies.

Comment 8: Line 340 in discussion – you have stated a study which contradicts your findings in that shock is a predictive factor for mortality – expand ref 46 and explain why current study might be different.

Reply 8: We apologize for the ambiguity caused by the unclear description; the study we cited also included shock as a predictor of mortality in VLBW infants. However, the specific definition of shock was not mentioned in that study.

Changes in the text: We have modified our text to make this clearer (see Page 11, line 285–286).

Comment 9: Can you include your protocol for intubation? Also I wonder why did you choose invasive mechanical ventilation yes or no and why not duration – clearly there is a huge difference in being ventilated for 24 hours compared to two weeks.

Reply 9: Indications for endotracheal intubation in the delivery room of EPIs are as follows: 1. effective positive pressure ventilation without clinical effect (heart rate, oxygenation not restored); 2. heart rate <60 bpm requiring chest compressions; 3. neonates with suspected diaphragmatic hernia or preterm infants with severe respiratory distress requiring administration of pulmonary surfactant (depending on the situation, some hospitals may use “INSURE” or “LISA”). Respiratory support is important for the prognosis of EPIs, and the type and duration of invasive mechanical ventilation and the parameter of ≥ 7 days of mechanical ventilation were included in the initial data of the study. However, since most preterm infants died within the first 7 days after birth, the duration of invasive ventilation is of little significance in predicting mortality.

Comment 10: I also suspect that severe RDS is co-linear with invasive ventilation as a binary outcome, please clarify.

Reply 10: We thank the reviewer for pointing out this issue. We apologize for some inaccuracies in the description of the statistical methods. These two indicators are both important for the prognosis of preterm infants, but they are indeed related. However, in the

multivariate regression analysis in this study, these two factors remained significant and directionally unchanged after mutual correction ($P<0.05$), so it is reasonable to assume that although these two indicators are correlated, there is no collinearity between them. Additionally, since the primary purpose of this study was to use stepwise regression analysis to construct a predictive model of mortality for EPIs, rather than to search for independent risk factors, and the results of the stepwise regression modeling showed that the inclusion of both indicators had a better predictive effect, we included both.

The above issues have been discussed with relevant statistical experts. They think that this procedure is reasonable. In the modeling process, it is also common to include indicators with correlations in the model.

Changes in the text: We have modified the inaccurate descriptions in the Methods section and added a discussion in the Limitations section(see Page 2, line 41; Page 6, line 156 and Page 11, line 301-305).

Reviewer B#

Comment 1: The authors analyzed risk factors for death before discharge in cohorts of preterm infants with a gestational age below 28 weeks cared for in several NICUs across various provinces of northern China. Gestational age, birth weight, severe cardiorespiratory disease (shock, pulmonary hemorrhage, severe respiratory distress syndrome) and therapeutic measure (chest compression in the delivery room, invasive mechanical ventilation) emerged as the best predictors of death before discharge. These findings are rather trivial, and the model to predict death before discharge is of limited value. However, the analysis took less than a quarter of infant deaths into account, as more than 75% of deaths occurred because parents abandoned their infants, apparently mostly for financial concerns. Apparently, most infants died for financial rather than medical reasons.

Reply 1: We thank the reviewer for reading our manuscript carefully and giving the above comments. It is worth noting that in this study, a significant proportion (43.2%) of preterm

infants with treatment abandoned were discharged from hospital with relatively stable vital signs and a chance of survival. Data regarding mortality of EPIs are valuable for these parents but the prognosis of EPIs in China cannot be predicted using existing prediction models due to great variations in conditions (including the level of economic development and medical care). We hope that through our efforts, the proportion of infants with treatment abandoned would gradually decrease in the future studies.

Comment 2: To make this analysis meaningful, the authors should analyze all four groups of infants (survival to discharge, death before discharge because of medical reasons, death because of parental abandonment, fate unknown because of transfer) and provide numbers for all variables analyzed for each of the four categories of infants.

Reply 2: We thank the reviewer for the valuable suggestions. We have added comparisons of total EPIs and dead EPIs between the two groups (complete and incomplete care).

Changes in the text: We added some data (see Page 7, line 182 to Page 8, line 195; eTable 1 and eTable 2 in the supplement) to describe the details of this subgroup. The results showed that the EPIs who received incomplete care (treatment abandoned by the parents before discharge) had a lower percentage of ANS, lower 5-min Apgar score, and higher percentage of invasive MV and pulmonary hemorrhage (all $P < 0.05$, eTable 1 in the Supplement). Comparing the clinical characteristics of EPIs who died at different time points (<7 days vs. ≥ 7 days) and in different groups (complete care group vs. incomplete care group), the EPIs who died at <7 days in the complete care group had a higher incidence of pulmonary hemorrhage (48.3% vs. 28.9%, $P < 0.05$), whereas among those who died at ≥ 7 days, the incomplete care group had a higher incidence of severe IVH or PVL (53.7% vs. 23.5%, $P < 0.05$, eTable 2 in the Supplement).

Comment 3: Furthermore, it is mandatory to also provide data of insurance status, health cost coverage and socioeconomic status and analyze their impact on survival, taking all infants with known death/survival status into account, Death because of parental abandonment is virtually unknown in cohorts of very preterm infants in neighbouring countries such as Japan, South Korea, or Taiwan, as well as cohorts in North America or Europe with universal health care coverage. The non-chinese reader should be given a

description on the way health care insurance works (or does not work) in China to better understand the strong impact of financial constraints on parental life-and-death decisions.

Reply 3: We thank the reviewer for this valuable feedback. We have revised the manuscript accordingly.

Changes in the text: We have modified our text as advised (see Page 4, line 75–83).