Assessment of epidemiological risk factors and clinical conditions for neonates in Cambodia

Hoang Long Ngoc Nguyen, Claudia Turner and Carol Anne Hargreaves

***Abstract*—Background: In developing countries, the commonest causes of death are due to the complications of preterm delivery, complications arising at the time of birth and from neonatal sepsis. In order to improve the outcome of unwell neonates, the epidemiology and mortality risk factors must be known.**

Methods: Using the hospital database all infants less than 28 days of age who were admitted to Angkor Hospital for Children (AHC) and the AHC Satellite Clinic (SC) from 1st January 2012 to 31st December 2013, subjective and objective clinical conditions at admission were analyzed. The microbiology laboratory database will be searched for all positive blood cultures obtained from neonates during the study time period and the bacterium that was isolated and its antibiotic susceptibility recorded on a Case Record Form (CRF). Depends on factor's measurement, Chi-square and KM curve are used to determine the significance.

Results: From 1st January 2012 to 31st December 2013, 54 out of 383 infants with full records of clinical signs and objective conditions died, giving an incidence rate of 14.1 per 1000 live births (95% CI 10.97-17.94). The risk assessment was carried out using Chi-square test and KaplanMeier estimator yield the 11 risk indicators: Birth weight, Gestation Category, Age at admission, Temperature, Oxygen Saturation, Respiratory Distress Category, Floppy, Apnoea, Seizure, Congenital Abnormality.

Conclusion: Clinical conditions of neonates admitted to AHC and SC differ from those in developed countries as important attributes are associated with sepsis, birth asphyxia and congenital abnormality. Those attributes can help to develop neonatal severity score for Cambodia as well as for regions with similar risk profile.

***Index Terms*—Neonatal mortality, epidemiologic risk assessment, pediatrics.**

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I. Introduction

Each year over three million neonates die, the commonest causes of death are due to the complications of preterm delivery, complications arising at the time of birth and from neonatal sepsis [1]. The majority of deaths occur in the first week of life and occur in the developing world [2] [3]. As 2015 approaches, strides have been made in working toward the fourth millennium development goal, the two thirds reduction in childhood mortality [4]. However this reduction has occurred mostly in children outside of the neonatal period [5].

Infections are the commonest cause of death in infants less than four weeks old [6]– [8]. Treatment, in a neonate with signs of sepsis needs to be initiated as soon as possible, before the causative organism is known. Empirical antimicrobial treatment relies on sound microbiological knowledge of organisms that occur in a population and of their antimicrobial sensitivity pattern.

In order to improve the outcome of unwell neonates, the epidemiology of the causes of morbidity and mortality must be known for a geographical region. With this information appropriate interventions can be explored and studies performed to evaluate impact. This study aims to describe the characteristics, diagnoses and outcomes of neonates admitted to AHC and SC over a three year period. These findings from risk assessment will be used to develop a severity scoring system which will be an invaluable tool for assessing the impact of the developing neonatal services at AHC and SC as well as for the evaluation of neonatal care intervention studies to be conducted in the future.

A. Introduction to Angkor Hospital for Children (AHC) and the AHC Satellite Clinic (SC)

Angkor Hospital for Children (AHC) and the AHC Satellite Clinic (SC) are non-governmental organization funded hospitals located in Siem Reap

and Sotnikum respectively. AHC has been providing free health care for children since 1999; it works within the Cambodian governmental health care system and is a recognisee teaching hospital. The hospital comprises of an outpatient department, inpatient department, emergency intensive care department and surgical departments. Over 500 children are seen each day. Its Satellite clinic was opened in 2010 and is located within the ground of the governmental referral hospital approximately 35km outside of Siem Reap city. Currently the neonatal services are in their infancy as both either AHC or SC are are developing them and the neonatal unit has now opened at AHC (12th September 2013) .

B. Data Collection

Using the hospital database all infants less than 28 days who were admitted to AHC or SC from 1st January 2012 to 31st December 2013 were identified. Hospital records for these infants are retrieved to complete study a Case Record Form (CRF) for each admission case. All study CRFs are anonymized and kept in a locked storage area. Each case is reviewed and a standardized diagnosis for each infant determined. The total complete cases is 383 records.

The rest of paper is organized as follows. Section II provides the background to risk assessment in developed and developing world as well as juxtapose and highlight the key distinctions between our data and current trend in neonatal epidemiology. In Section III and IV , we explore and understand data at descriptive and prescriptive level. We summarize our conclusion and further research in Section V.

II. Literature Review

In the last 20 years, Cambodia's neonatal mortality rate (deaths in the first 28 days of life per 1000 live birth) has dropped significantly [9] from 37 in 1990 to 18.4 in 2012. Similarly, the mortality rate for under-5 children per 1000 has decreased from 116.4 to 39.7 within the same year span. According to UN Millennium Development Goal 4 (MDG 4), Cambodia has met the goal set by United Nation 14 years ago as its child mortality rate has been cut by two third. However, the reduction is uneven among different group: while most of the decrease is seen in older children within the group, neonatal mortality has since witnessed slow progress and lesser development. In 1990, only 32% of under-5 death comes from neonatal but in 2012, the proportion has climbed up to 46%. The shift in children mortality, on the other hand, follows the developing world trend: the proportion of under-five deaths that occur within the first month of life (the neonatal period) has increased 17 percent since 1990, from 36 percent to about 43 percent in 2012, because declines in the neonatal mortality rate are slower than for older children [10].

From the WHO's regional groupings for Millennium Development Indicators, Cambodia belong to Developing region and South-eastern Asia. However, there is a substantial discrepancy between these two regions: the child mortality rate in 2012 was 57 and 29 respectively. Within the same sub-division, the country performs worse than its neighboring nations but fares significantly better than the average of developing world in aggregate. Due to vast variation in mortality rate among regions, a health promotion and intervention for developing world unlikely works well in Cambodia, thus it requires the planning and intervention must come from a national, or even better, provincial level.

III. Cambodia's neonatal mortality risk assessment

A. Causes of Death

The cause of death in neonatal around the world varies from region to region as shown below

TABLE I
Causes of neonatal mortality

Cause	Cambodia	Our data	Europe	South East Asia
Preterm birth complications	31.5	36	37	37
Neonatal sepsis	21.7	33	8	17
Birth asphyxia	28.7	15	16	19
Congenital abnormalities	6.6	9	20	9.6
Other	11.4	8	20	17

The reported figures of Cambodia, Europe and South-east Asia are referenced to [1]. Our data broadly reflects the proportions reported by WHO and national statistics. The higher percentages in neonatal sepsis and lower in birth asphyxia can be explained by the fact that our data sampled from the most advanced children hospital in Cambodia and most admitted cases are related to post-delivery complication and acute infection. However, the total

percentage of these two categories are similar with 40.4% and 38% for census data and our data, respectively. It shows that the proportion of non-congenital death causes of our data is consistent with national numbers while preterm birth complication, congenital abnormality and other causes are similar with reported data. Thus it assures us the collected data essentially does not deviate from the population.

Compared to developing countries like Europe, the admitted patient profile is very different in which there is only 9% of cases in the our data died due to congenital abnormality whereas the figure is 20% in developed world. On the other hand, the there is 4 times more of cases died from sepsis in AHC and SC than in Europe. Such contrast requires very different public health strategy to deal with neonatal mortality and since the patient profiles are different, severity score and risk models built using developed country's data such as CRIB or SNAP cannot be used.

However, it is important to point out that even though infection (sepsis and skin infection) is not always preventable, it is certainly possible to reduce the number of deaths from it. The reduction in neonatal sepsis will bring mortality rate down by at least 5–15% if compared to neighboring countries or 15–25% if compared to developed world standard. Because it is difficult to diagnosis sepsis signs and symptoms, even at the most advanced clinical settings, the ill neonates may not be detected. These are really explanations as to why neonates die from infection is not the cause. The cause is either from mother during delivery or from the environment (including family) after three days of age. On the other hand, the causes of infection can be attributed such as under-recognition of illness, delay in care seeking or detected too late at the household level, lack of access to both appropriately trained health workers and to high quality services to manage sepsis [8]. There are few suggestions to tackle the issues of delayed treatment of neonatal sepsis in which public health program can play an integral part such as management of neonatal infections in community setting [11]. In other papers, [12] [13] proposes available data on the use of oral and injectable antibiotics for the management of neonatal sepsis. Such preventive medicine can be an effective tool to reduce the neonatal mortality due to infection and requires further research in health services and epidemiology to make it a successful intervention.

B. Age of Death

The assessment on age of death shows the similarity in structure but difference in magnitude. Figure 1 illustrates the daily risk of death during the first month of life Figure 2 depicts the global statistics based on household responses [2] from multiple sources. The difference in magnitude does not indicate great difference as all the neonates admitted to our data have high risk of death as to compared to ordinary cases with low risk. However, there are some insights gained from these 2 charts:

1) The risk of death is at maximum within 24 hours of death, which account for 20% of neonatal death in our data. However, global data reports even higher percentage, which stands at 25-45%.
2) Both curve exhibits exponential decay though our curve is rather more rugged due to less sample size. Yet, the curve from our data is fatter and does not die down quickly. It shows that these babies could have been admitted to the hospital earlier and received better care. While the majority of death in the first week is due preterm birth complication and birth asphyxia, which accounts for 45.8% and 17% respectively, the leading cause of death after the first week is in fact due to neonatal infection which accounts for 55.8%. The change in proportion is shown in Figure 3. The later death proportion indicates that these neonates could have been acquired sepsis but was not diagnosed early thus offers good opportunity for early detection to provide these newborn on time medical assistance. Also, the older baby is might mean that it has been admitted longer so more likely to be pre-term, which is a big risk factor for sepsis.

The problem with sepsis can be underestimated as a high percentage of babies are delivered and die at home without ever being in contact with trained health care workers and therefore without ever reaching the statistics. In developing countries, the rate of home deliveries is high, and the percentage of deliveries assisted by a skilled attendant is low [6]. The problem of post-natal hygiene care and birth delivery sanitary could have been overlooked.

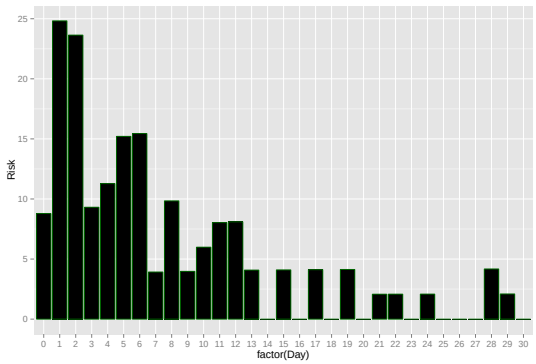

Fig. 1. Daily Risk of death from our data

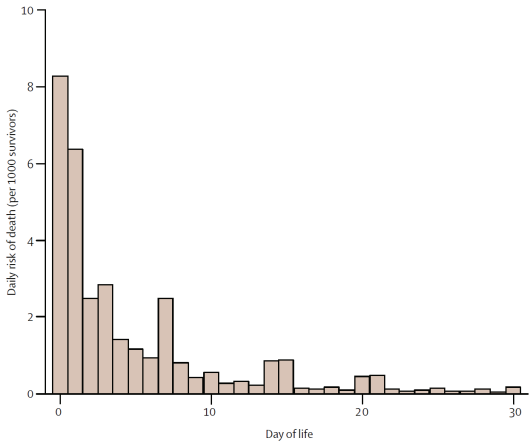

Fig. 2. Daily Risk of death from global data

Moreover, there are many who do not have the access to medical treatment due to their parents stay in rural area which impedes the timely treatment.

C. Preterm gestation

Given largely missing value in exact gestation period, we turn our focus to gestation category (either term or preterm). The cross-tabulation for gestation category (term with gestation more than 37 weeks and preterm otherwise) and mortality rate is:

TABLE II
PRETERM GESTATION AND NEONATAL MORTALITY

	Survived	Death	Row Total	Mortality Rate
Term	263	30	293	10.2
Preterm	66	24	90	26.7
Column Total	329	54	383	14.1

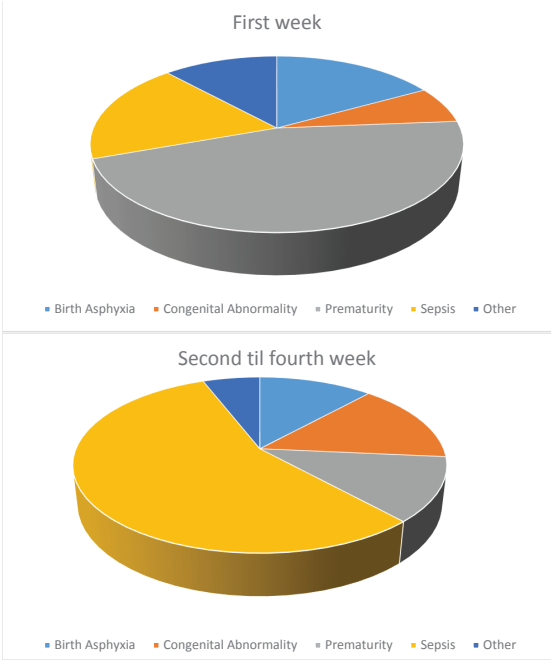

Fig. 3. Comparison between cause of death in neonates within the first week and the rest of first month

The Chi-square test results X-squared = 14.0154 with 1 degree of freedom and p-value = 0.0001813 which clearly proves that there is a clear difference in gestation category and death rate.

D. Low birth weight

By setting 3 threshold for birth weight by convention as: Normal (birth weight more than 2.5 kg), Low birth weight (less than 2.5 kg), Very low birth weight (less than 1.5 kg), the Pearson's Chi-squared test with Yates' continuity correction performed on mortality risk versus birth weight band shows X-squared = 24.6381 with 2 degree of freedom and p-value = 44.466e-06. Thus at 95% confidence we can conclude that there is significant difference between death rate and birth weight. Cross-tabulation with column and row percentage are:

TABLE III
BIRTH WEIGHT AND NEONATAL MORTALITY

	Survived	Death	Row Total	Mortality Rate
Normal birth weight	217	22	239	9.2
Low birth weight	91	18	109	16.5
Very low birth weight	21	14	36	38.9
Column Total	329	54	383	14.1

Figure 4 illustrates KM curve and it is obvious

that "Very Low birth weight" group have the highest risk of mortality with survival rate at 30th day of postnatal age is only 40%. On the other hand, "Normal birth weight" group has substantial higher survival rate at 90% within the same period.

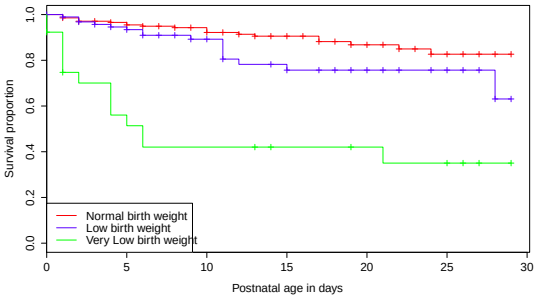

Fig. 4. Kaplan-Meier survival plots for birth weight divided into categorical bands

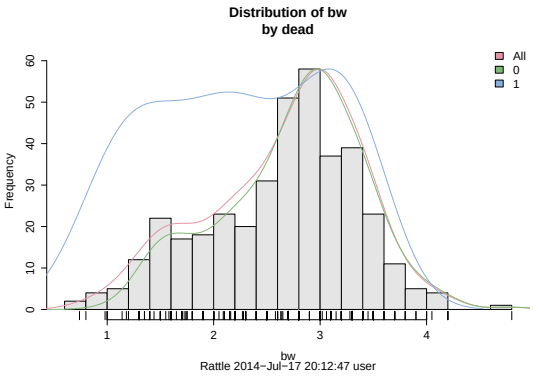

Fig. 5. Histogram for birth weight

To investigate further the high risk of low birth weight, a Cox proportional hazard model was constructed and the fitted model exponential coefficient for "Low birth weight" and "Very Low birth weight" are 1.94 (p-value: 0.0376) and 4.576 (p-value: 1.71e-05) respectively. The odd ratios show that those with birth weight less than 1.5 kg have 4.5 times higher of mortality compared to those with weight more than 2.5 kg. The histogram in Figure 5 also shows a flat, wide distribution of dead neonates' birth weights while those survived has a peak at 3 kg. The different in two distribution again confirms that birth weight indeed can help to predict the mortality.

E. Temperature

There are two abnormal clinical symptoms related to temperature that can be found in infant with less than 28 days of age: Hypothermic (Temperature less than 36.5 Celsius degree) and Fever (Temperature higher than 38.5 Celsius degree). Within 36.5 and 37.5, we have normal range.

TABLE IV
HYPOTHERMIC, FEVER AND NEONATAL MORTALITY

	Survived	Death	Row Total	Mortality Rate
Normal Temperature	128	11	139	7.9
Fever	34	4	38	10.5
Hypothermic	167	39	206	18.9
Column Total	329	54	383	14.1

Even though p-value is 0.0125 and shows significant association between temperature and mortality, we need to explore further as there are very few cases with fever. The fitted Cox model confirms that fever category is in fact, insignificant (p=0.541) despite having odd ratio of 1.43. In contrast, hypothermic symptom is both statistically significant (p=0.000768) with odd ratio of 3.16. The survival rate seen in Figure6 tells different story: the admitted babies with Fever or Hypothermic condition on arrival does not succumb quickly (less than a day) but the dead happened at much later age (as the drop in survival rate is gradual, not abrupt). Such evidence prevents us from conclude that there are clear association between temperature and mortality. On the other hand, those with fever have similar risk profile compared to those having normal temperature whereas neonates with hypothermic have lower survival chances than the other two. The temperature histogram in Figure 7 provides a further confirmation on the different between those survived and those who are not. It can be seen quite clearly that the temperature for those who passed away have significant lower temperature with higher variance while those alive have a high kurtosis peak at 37 degree.

IV. OTHER OBJECTIVE CLINICAL ASSESSMENTS

Our data also include other clinical assessments which can help to determine well-being of admitted infants: Tachypnoea (Respiratory rate higher than 60 per minute), Tachycardia (Heart rate faster than 160 per minute), Hypoxia (Oxygen saturation less

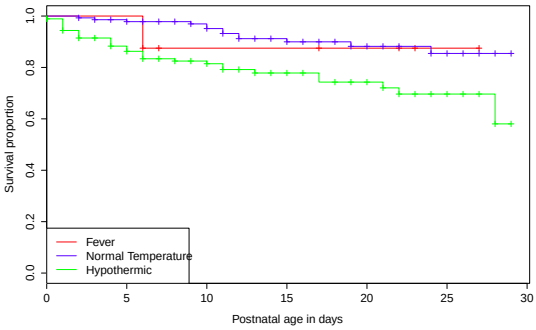

Fig. 6. Kaplan-Meier survival plots for temperature divided into categorical bands

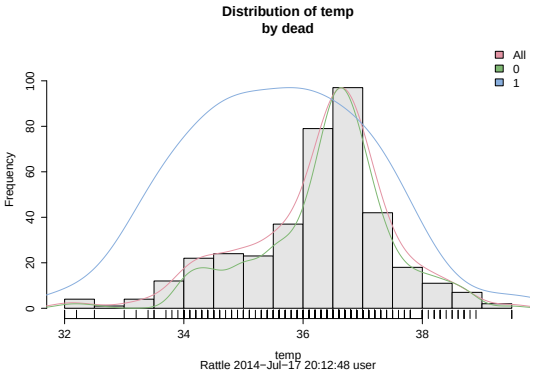

Fig. 7. Histogram for temperature

than 92%) and Hypoglycemia (Blood sugar less than 2.6mmol/L). For each condition, cross-tabulation, Chi-square, KM curve and Cox model are carried out.

A. *Tachypnoea*

TABLE V
TACHYPNOEA AND NEONATAL MORTALITY

	Survived	Death	Row Total	Mortality Rate
Normal Respiratory Rate	245	38	283	13.43
Tachypnoea	84	16	100	16
Column Total	329	54	383	14.1

There is only slight distinction in mortality rate between tachypnoea (16%) and normal breathing group (13.43%). The hypothesis is further assessed by Chi-square test shows that there is no statistical significant association between tachypnoea and mortality at 95% confidence as p-value is 0.6396. The weak relationship between tachypnoea and mortality is then reaffirmed by Cox proportional hazard model as the coefficient falls into rejection region (p=0.645). Together with cross-over KM curves showed in Figure 8 it is clear that the condition does not influence neonate's risk and hence it should be excluded. To reaffirm our exclusion, a histogram was fitted and showed in Figure 9 which do not show any difference in respiratory rate distributions between two assessed groups. Hence we will not consider respiratory rate as an important risk factor.

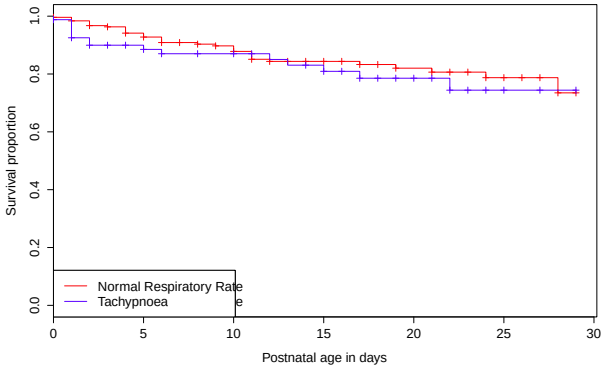

Fig. 8. Kaplan-Meier survival plots for tachypnoea and normal condition

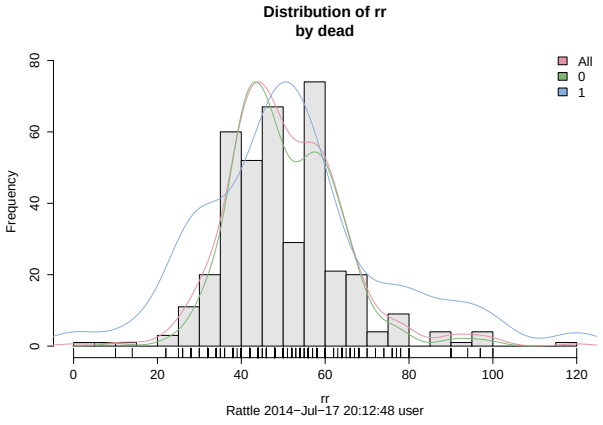

Fig. 9. Histogram for respiratory rate

B. *Tachycardia*

The condition is known for heart rate faster than 160 bpm. Together with other clinical assessments, a categorized version of heart rate is a weak statement

to conclude the mortality rate as the reading is recorded at admission and subject to fluctuating variations.

TABLE VI
TACHYCARDIA AND NEONATAL MORTALITY

	Survived	Death	Row Total	Mortality Rate
Normal Heart Rate	277	41	318	12.9
Tachycardia	52	13	65	20
Column Total	329	54	383	14.1

Chi-square statistics is 1.7021, corresponding to p-value of 0.192 which means that the symptom does not significantly associate with fatality rate. The Cox proportional hazard model's tachycardia coefficient is also insignificant (p=0.548)and KM curves in Figure 10 show no dominance in survival probability between normal condition and rapid heart rate. Similar to respiratory rate, heart rate histogram showed in Figure 11 does not show any visually different in two group's heart rate, thus strengthen our hypothesis that heart rate is not an evident risk indicator.

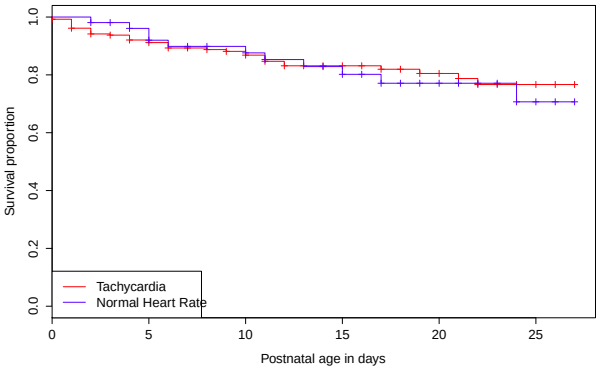

Fig. 10. Kaplan-Meier survival plots for tachycardia and normal condition

C. Hypoxia

Oxygen saturation indicator alone offers much insights into the mortality rate: there are many reasons why a baby might be hypoxic - pneumonia, congenital heart disease. However, cerebral hypoxia-ischemia, defined as partial lack of oxygen to the brain, is the most frequent cause of seizures (hypoxia leads to brain damage which causes seizures) in the newborn period [14]. As such, hypoxia indicates

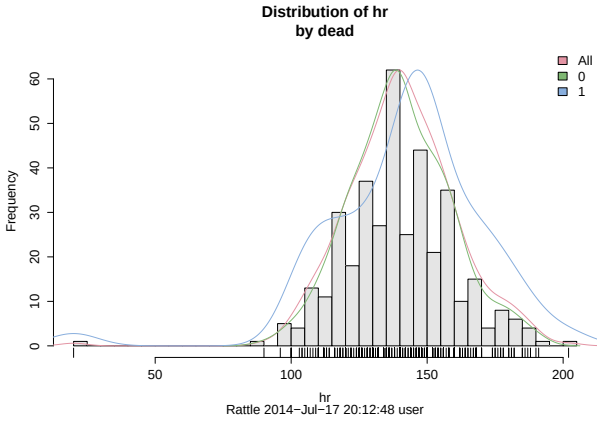

Fig. 11. Histogram for heart rate

the high risk of not only in mortality but underline the chance of morbidity in neonates. Our data shows that 26.7% cases of hypoxia eventually died which is comparable with other sever condition such as "Preterm gestation"

TABLE VII
HYPOXIA AND NEONATAL MORTALITY

	Survived	Death	Row Total	Mortality Rate
Normal Oxygen Saturation	277	35	312	11.2
Hypoxia	52	19	71	26.7
Column Total	329	54	383	14.1

The condition is statistically significant (p-value-0.001388) and its odd ratio in Cox model is 2.77(p=0.000356). Similarly, survival rate of newborns with the symptom is also lower as seen in Figure 12. However, the histogram plotted in Figure 13 do not show a clear distinction due to dense scale.

D. Hypoglycaemia

TABLE VIII
HYPOGLYCAEMIA AND NEONATAL MORTALITY

	Survived	Death	Row Total	Mortality Rate
Normal Blood Glucose	297	44	341	12.9
Hypoglycaemia	50	10	206	16.7
Column Total	329	54	383	14.1

Chi-square test with p-value of 0.6743 affirms that there is no statistical significant association between hypoglycaemia and mortality. Note that the

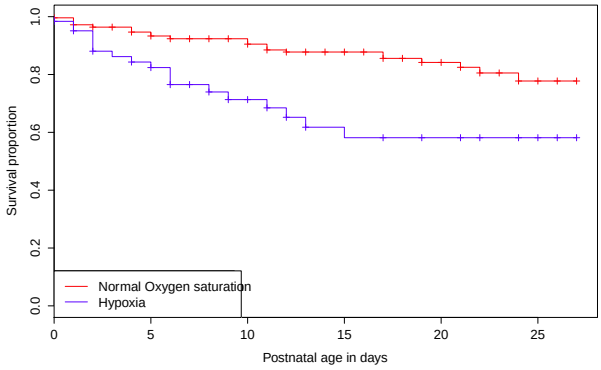

Fig. 12. Kaplan-Meier survival plots for hypoxia and normal condition

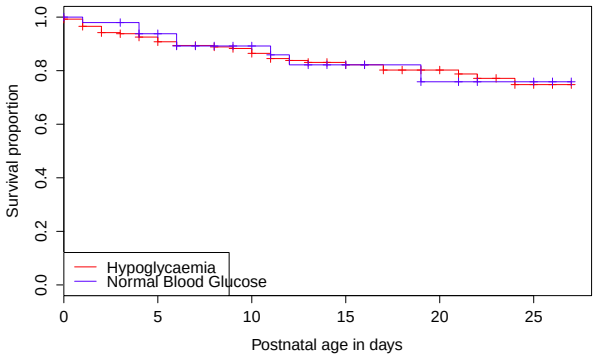

Fig. 14. Kaplan-Meier survival plots for hypoglycaemia and normal condition

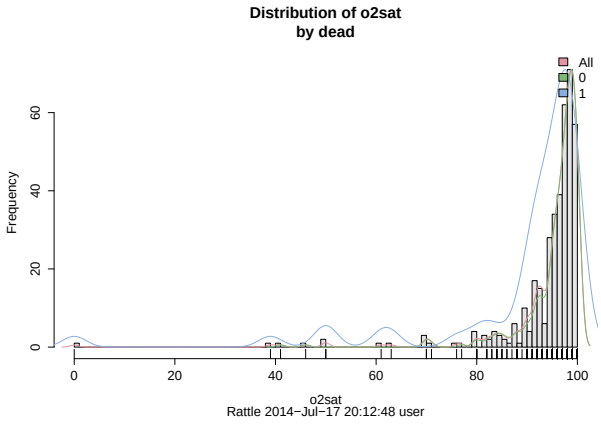

Fig. 13. Histogram for oxygen saturation

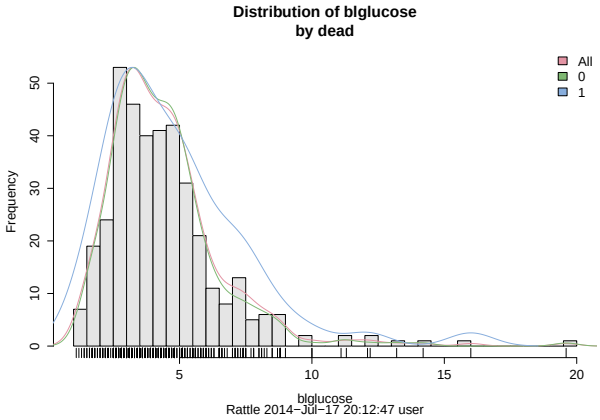

Fig. 15. Histogram for blood glucose

mortality rates between normal condition and low blood glucose are marginally different as well (12.9 vs 16.7). Furthermore Cox model reconfirms that hypoglycaemia is indeed insignificant (p=0.634) and KM curves depicted in Figure 14 shows that survival rate curve of hypoglycaemia intertwines with normal condition's. Thus we can remove this variable in modeling process. The two distributions of dead and survived groups graphed in Figure 15 almost merge together which manifests that the difference is relatively identical.

E. Subjective clinical assessment

Contrast to objective clinical indicators which relies on measurement and other recorded metrics, subjective clinical assessments is based on observation and varies depending on doctors. The table below summarize 5 key indicators that were recorded in our data (** indicates statistical significance):

TABLE IX
OTHER SUBJECTIVE AND OBSERVATORY ASSESSMENT VS NEONATAL MORTALITY

	Survived	Death	Row Total	Mortality Rate	p value
Floppy	18	15	33	45.4	2.5e-07**
Shallow breathing	16	5	21	23.8	0.32
Respiratory Distress	79	31	110	28.8	1.1e-06**
Apnoea	25	13	38	34.2	4.5e-04**
Seizure	8	6	14	42.9	5.8e-3**
Jaundice	99	15	114	13.2	0.854
Congenital Abnormality	25	10	35	28.6	0.02**
Twin	6	4	10	40	0.054
Male	192	26	218	11.9	0.21
Female	137	28	165	17	0.21

Based on Chi-square test, the selected clinical assessment variables are: Floppy, Respiratory Distress, Apnoea, Seizure, Congenital Abnormality. Together with Gestation category, Oxygen saturation, Age at admission, Temperature and Birth weight, we have chosen 10 variables suitable risk indicators as well as attributes for development of neonatal severity score.

V. Conclusion

In this paper, an assessment epidemiological risk factors and clinical conditions was carried out to highlight and ascertain the role of key risk factors related to neonatal mortality in Siam Reap, Cambodia. Continuing from the literature review done in Introduction, Section II elaborates about infant dead rate, specifically on neonatal risk assessment available in the literature and existing reports to highlight the possible root causes and current trend in Cambodia as well as the world. Based on information gained in this section, the subsequent chapter is devoted entirely in order to describe the epidemiological risk factors for death in infant admitted at AHC and SC. There are many insightful facts such as the causes of death largely follow the national trend and being consistent the patterns of developing world, though the higher of reported sepsis cases does suggest a better attention to the medical care quality and prevention. The admitted patients at the clinics and hospitals die at the later age of post-natal days than the average of the world. Coupled with high proportion of sepsis, the finding recommends a better management of hygiene and early detection of infection to fight against infant mortality and improve medical care in children. However, the recommendation should be taken with a pinch of salt: as not all are hospital acquired infection, and even those cases that are detected early die if it is a severe case or the bacteria causing the infection is antibiotic resistant. Even though the neonates' cases reported in our Cambodia data set generally have slightly lower birth weight compared to US newborns, majority of admitted cases have appropriate weight for gestation when it is benchmarked against developed's word data.

Another significant contribution of our research is to determine important clinical and subjective assessment to the mortality rate from the data. These features can provides medical doctors better understanding toward current admitted cases at the hospital. Our insights illustrate numerous indicators related to NMR, which must be heeded if neonatal survival is to be improved. Hypoxia, Floppy, Respiratory Distress, Apnoea, Seizure are also tested to be important attributes in predicting dead rate in infant less than 28 days of age. These conditions were not included in established severity score model yet related to mortality in Cambodia where neonatal sepsis is prevalent.

Future researches can utilize the important factors and their association with each other described in this paper to revise a predictive model which can help to assess the mortality risk of admitted cases, based clinical conditions at admission.

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