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Late-onset neonatal sepsis in Dar es Salaam, Tanzania: a prospective-cohort, clinical research study.

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Abstract.

Background: *Late-onset neonatal sepsis* is evidently associated with more hospitalization and deaths than even early onset neonatal sepsis. Most studies on neonatal sepsis in metropolitan areas of sub-Saharan Africa were underpowered to get reliable estimates of the burden.

Objective: To assess incidence and factors associated with *late-onset neonatal sepsis* among newborns admitted at Dar es Salaam regional referral hospitals.

Methods: A prospective cohort, analytical hospital-based study was conducted at all Dar es Salaam public regional referral hospitals. Newborns (≥ 3-days old) with *presumptive diagnosis of late-onset sepsis* were the target population. Neonates (≥ 3-days old) with other diagnoses were considered as controls. Data were collected using a pre-designed Case Report Form. A multivariable binary logistic regression model was fitted to account for factors associated with *presumptive diagnosis of late-onset neonatal sepsis*.

Results: We recruited and analysed 9821 neonate-days of follow-up. Incidence of late-onset neonatal sepsis was 26.8 per 1000 livebirths. Presumptive late-onset neonatal sepsis was found in 61.6% of target population. Newborns with *presumptive diagnosis of late-onset sepsis* were more likely to die than

newborns with other diagnoses (Mann Whitney U = 398.7, p=.000). Grunting (A.O.R.: 5.285 (95% C.I.: 2.179 – 12.82), history of foul smelling liquor (A.O.R.: 10.4, 95% C.I.: 1.16 - 92.4) as well as effect modifiers/interaction between hospital site vs. hospital where the child was born (Amana*Amana – A.O.R.: 0.48, 95% C.I.: 0.41 – 0.68; Mwananyamala* Mwananyamala – A.O.R.: 1.01, 95% C.I.: 1.00 – 1.746) were factors significantly associated with probability of late-onset neonatal sepsis.

Conclusion: Late-onset neonatal sepsis was highly prevalent in this study population.

Recommendations: Timely hygiene-based intervention strategies need to be applied for effective reduction/elimination of late-onset neonatal sepsis.

Keywords: Newborn, sepsis, presumptive diagnosis

Introduction.

The first 28 days of life have been considered as the most crucial, as it is the period when a child's survival is most vulnerable. However, global health systemic efforts are still incongruent to its intended results, given the unacceptable higher rates of newborn deaths worldwide to date [1-3]. Neonatal sepsis stands among significant and top global health agenda associated with neonatal deaths worldwide [4-6]. In Low and Middle Income Countries, data suggest up to 70% of all newborn deaths to be attributable to sepsis [4]. Neonatal sepsis has been classified as *early-onset* or *late-onset* dependent on age of onset and/or timing of onset [7]. Late-onset neonatal sepsis refers to *a systemic condition of bacterial, viral or fungal origin that are associated with haemodynamic changes and other clinical manifestations that occur after 72nd hour of extra-uterine life on earth* [7, 8]. This clinical definition is not without reservations. In fact, even the definition of neonatal sepsis in general is still debatable and inconclusive by far worldwide even to the present day [6, 9]. This study was derived to address the burden and factors associated with the domain of *late-onset neonatal sepsis* at typical metropolitan hospital settings of East Africa.

Late-onset neonatal sepsis gains significant interests among clinician-scientists, practicing neonatologists and even demographers with interest in morbidity and mortality statistics the world over. It often results into more mortality risks, prolonged hospitalization as well as even more neurodevelopmental risk outcomes compared to early-onset neonatal sepsis [10-13]. There are circumstantial, epidemiological and even potentially philosophical mysteries behind the current proposed *late-onset neonatal sepsis* definition. For instance, whereas it is relatively a common understanding that what constitutes current proposed definition of *late-onset sepsis* among newborns to be sequelae of primarily extra-uterine environment, there are growing body of literature that endeavours to suggest even the microbial floral patterns between what goes on as early to late-neonatal infections to be indistinguishable [7].

Moreover, on epidemiological grounds, the challenges of dichotomizing the definition based on time resulted into another conundrum since in some cases, organisms causing late-onset neonatal sepsis have been found to be from the time of parturition but with clinical manifestation after 72-hours of extra-uterine life. Thus, it has proved illogical to ascertain *early* vs. *late-onset neonatal*

sepsis especially among those born with extremely low gestational age and even high risk term infants solely based on the factor of time [7]. Besides, there are contextual differences with philosophical arguments that caution against distinguishing *early* vs *late neonatal sepsis* based on time of onset alone. For instance, for those newborns who were born extremely low gestational age and even those high risk term newborns, many of whom have prolonged hospital stays, the concept of *late-onset neonatal sepsis* has been referred to any episode(s) of blood-born or CSF infection from birth to hospital discharge, regardless of age at the time of onset [7]. In this study, we endeavoured to characterize the burden and associated factors of *late-onset neonatal sepsis* using presumptive symptoms/signs of sepsis in newborns

Previous studies from Tanzania revealed variable burdens of sepsis in newborns [14-17]. However, they were all based on point prevalence of *late-onset neonatal sepsis*, with none on incidence rate [14-17]. For instance, whereas the study by Mhada and colleagues reported a point prevalence of *late onset neonatal sepsis* of around 29.7% [14], Kayange and others study findings revealed a point prevalence of up to 70% [15]. However, both studies had significant and potentially irreparable errors in their methods and even results sections. For instance, whereas Mhada's findings likely under-estimated the true burden of *late-onset neonatal sepsis* since their threshold was from older children (≥ 7 days old) [15], the study by Kayange and colleagues from Mwanza in Tanzania had serious overt design errors [16]. Specifically, they reported their study design to be "cross-sectional, prospective study" [16], something that is at best a confusion from epidemiologic viewpoint! Moreover, through their reported sampling strategies, it was not possible to rule out referral bias; leave alone their entire study goal probably fell short of its intended meaning (prediction) [16]. Thus, the need for fresh data with remedial measures in design and even data presentation sections.

Several published studies specifically associated with *late-onset neonatal sepsis* have been retrieved in literature [10, 11, 13, 18- 21]. However, only one was retrieved from Africa (22) and none specifically from Tanzania. The African study was from Ethiopia and revealed maternal urinary tract infections/sexually transmitted infections (A.O.R.: 9.4, 95% C.I.: 3.1 – 28.5), preterm delivery (A.O.R.: 4.9, 95% C.I.: 1.7 – 13.7), mixed type of infant feeding/formula feeding before admission (A.O.R.: 12.7, 95% C.I.: 3.7 – 42.8) as well as usage of endotracheal/mechanical intubation (A.O.R.: 8.3, 95% C.I.: 1.8 – 26.4) to be statistically significantly associated with late-onset neonatal sepsis using a case-control study [22]. However, the study sample were derived using consecutive sampling (a non-probability sampling scheme) and hence questionable generalizability. Besides, the study was severely underpowered for determinants of late-onset neonatal sepsis with clear evidence from wider confidence intervals in almost all estimates. We thus considered timely to design a prospective cohort study to estimate prevalence and associated factors of late-onset sepsis among neonates admitted at Dar es Salaam public regional referral hospitals.

Methods

Study design:

A prospective-cohort, observational, hospital-based analytical study with 1: 1 matching by age (+/- 2 days) a brief follow-up of participants from any time after 7th day up to their 28th days in order to determine early clinical outcomes of sepsis.

Study settings:

Dar es Salaam public regional referral hospitals. Specifically, the study was conducted at Amana, Mwananyamala and Temeke hospitals. They are the only public regional-level hospital facilities with specific neonatal units in Dar es Salaam. Dar es Salaam city is among the rapidly growing metropolitan cities in Africa. The city is rich in demographic population prominent in African settings, ranging from Bantu, to Afro-Shiraz as well as Nilotic sub-population available in today's Tanzania. Tanzania has been cited to be the fastest country in terms of her demographic transition process in entire Africa [23].

Study population:

All neonates ≥ 3-day old admitted in the neonatal units at representative Dar es Salaam hospitals.

Target population:

All neonates ≥ 3-days old with presumptive diagnoses of neonatal sepsis.

Sampling technique and sample size determination:

Census based approach was used since all neonates who met eligibility criteria at the study sites during the study period were recruited and analysed. Neonates were eligible to be included into the study provided that they were at least 72-hours old, admitted at either Amana, Mwananyamala or Temeke regional referral hospitals either as self-referrals or referred from lower level facilities. Besides, for all neonates who constituted as *cases*, they either had presumptive symptoms/signs of sepsis as per Tanzania's national guidelines for neonatal care definition of sepsis. Otherwise, neonates ≥ 72-hours old admitted due to other diagnoses constituted as *controls*. All newborns whose presumptive symptoms/signs were derived before 72nd hour on earth, those whose symptoms/signs necessitated referral to Muhimbili National Hospital were excluded from this analysis.

A minimum sample size of around 384 neonates had a power to detect *late-onset neonatal sepsis* of at least 80% given the apriori α-level of 5% considering the prevalence of 50%. The decision to set the prevalence of *late-onset neonatal sepsis* at specific 50% lies on the fact that, of all published studies on neonatal sepsis in Tanzania, none was specifically powered to detect *late-onset neonatal sepsis*. Moreover, in order to account for uncertainty, investigators allowed for a non-response/missing data rate of up to 10% and added up to the calculated minimum sample size of 423 neonates. Thus, at least 423 neonates older than or equal to 3 days (≥ 72 hours) old were to be recruited in order to specifically detect the point prevalence of *late-onset neonatal sepsis* in Tanzanian hospitals.

Data collection tool:

A pre-designed Clinical Research Form (CRF) was uploaded in the AfyaData App, then installed in smartphones to collect data from mothers/caregivers. It was used to assess factors associated with *late onset neonatal sepsis* among ≥ 72 hours old neonates. The tool consisted of four parts namely; *socio-demographic characteristics* (i.e. neonate's date of birth, place of residence, birth order as well as neonate's sex. Part II: *Neonatal factors* (birthweight, Apgar scores at 1st and 5th minute, respiratory rate on admission, temperature on admission, presumptive symptoms/signs of sepsis on admission, +/- congenital anomalies, singleton/multiple children). Part III: *Maternal factors* (i.e. number of recorded antenatal visits on RCH card, parity, number of living children, marital status, highest level of

education, maternal date of birth, +/- maternal fever, mode of delivery, gestation age at delivery, duration of labour, history of infections in last trimester/labour time, +/- multimorbidities). Part IV: *Hospital factors* (presence of mechanical ventilator, total parenteral nutrition and prolonged use of central venous catheters, +/- neonatologist's consultation for index child, +/- emergency surgical interventions)

Data collection tool pre-testing:

Prior to data collection, both tool test reliability and validity was assessed using a pilot study conducted at Kairuki hospital emergency and paediatric wards. Specifically, 45 mother-neonate pairs were used to assess for test-retest reliability as well as content validation analysis of the research tool.

Data collection procedures:

Data were collected by six research assistants (two nurses at the neonatal units of each hospital) and the principal investigator. Every newborn admitted to the neonatal units at the study sites was recruited if the mother consent to take part in the research until the sample size will be reached. The data obtained was on socio demographic data of the neonates, neonatal related factors, maternal related factors and hospital related factors. National Guideline for Neonatal Care and Establishment of Neonatal Care Unit by the United Republic of Tanzania (2) was used to assess neonates with clinical sepsis.

The following clinical characteristics were used to define presumptive symptoms/signs of sepsis. Specifically, a presumptive diagnosis of sepsis was made to any newborn if: - *fast breathing (> 60 breaths /min)*, *grunting*, *severe lower chest wall in-drawing*, *cyanosis*, *temperature – fever > 37.5 °C or Hypothermia < 36.0°C*, *prolonged capillary refill time (CRT)*, *not feeding well*, *convulsions, drowsiness* or *unconsciousness*, *movements upon stimulation only* or *no movements at all*.

An interview of mothers with each enrolled neonate were conducted by trained research assistants and/or the Principal Investigator. Each participant was interviewed in privacy to promote confidentiality. A thorough physical examination was done to all newborns. Parameters such as head circumference, weight, and length, were taken prior to the examination. Then skin, head and neck, heart, and lungs of the newborn, abdomen and genitalia, and nervous system and reflexes were next examined by the principal investigator and the research assistants. Lastly, for each studied neonate, at least 5 cc of venous blood was collected for both blood-based aerobic and anaerobic culture analysis at each of the facilities laboratory. Gram staining and standard biochemical staining methods were applied to identify microbial isolates. Disc-diffusion technique was applied to screen for drugs susceptibility tests for 10 frequently used antibiotics. Specifically, it analysed '*minimum concentration of inhibition areas*'. The results of blood culture and sensitivity analyses were subsequently used for verifying (rule in/out) the presumptive symptoms/signs of sepsis made earlier. Moreover, each recruited child was followed-up until day 28th of life or death (which ever came first) with subsequent re-admission also analysed if separate from earlier admission for their microbial floral patterns.

Variables definition:

Dependent variable: Proportion of neonates with newly presumptive symptoms/signs of late-onset sepsis

Independent variables:

Independent variables were categorized into four (4) distinct categories, namely: *social demographic*

characteristics, *neonatal factors*, *maternal factors* and *hospital/system-related factors.*

Adjustment variable: Hospital where the babies were born

Data management and analysis:

Data once collected was triple entered into SPSS version 23 (SPSS™, IBM – New York, USA) template and later stored in the PI's laptop until analysis time. Initial data cleaning was performed daily immediately after entry. They included checking for errors (e.g. duplicates, missing data – both item and/or unit missingness) as well as authenticating validity of collected data. For all instances of missing data, efforts were made to go back and record/retrieve the missing part, either via phone calling mothers and/or cross-checking with hospital files information. Data analysis commenced by exploratory data analysis. Specifically, analysis of linear trends, patterns (e.g. significant correlations, etc) as well as data summarization were assessed. Contextually, all categorical data were summarized using count and proportion (by %) while continuous data were summarized using median (with corresponding inter-quartile range). Finally, Statistical Package for Social Scientists (SPSS ™) version 23 statistical software (IBM Business analytics, NY-USA) was employed to conduct data analysis. *Chi-Square test for independence* was used to compare statistical differences among categorical variables, and *independent T-Test* was used to compare statistical differences among continuous variables. For some select few continuous/discrete variables that were followed-up, comparative statistics were made using a non-parametric test (Mann-Whitney U test). Multivariable binary logistic regression analysis model was fitted to account for significant factors associated with late-onset neonatal sepsis after appropriate validation of linear model assumptions. Specifically, each independent variable was regressed against outcome variable (i.e. late-neonatal sepsis status, dichotomized as 1 = 'late-neonatal sepsis evident' and 2 = 'neonates ≥ 3 days with other diagnoses') for possible *normality*, significant *multicollinearity*, *autocorrelation*, *linearity*, *independence* as well as *homoscedasticity*. Both univariate and multivariable binary logistic regression analysis were conducted and findings expressed as odds ratios. For a candidate model to be included into the multivariable model, a p-value <0.2 was used as a limit. For final multivariable analysis, a p-value <0.05 was used as a limit of type 1 error. Tests for interaction (effects modification) among selected clinically and health system-based relevant variables were also tested.

Ethical clearance and permission to conduct the study at study sites:

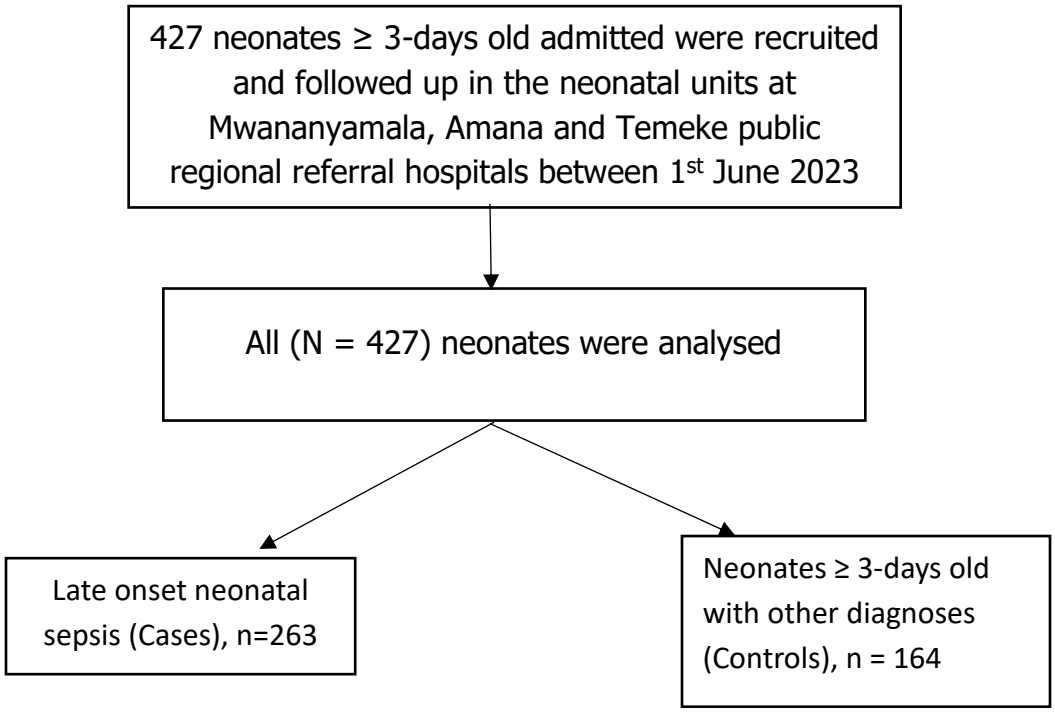
Ethical clearance (HKMU/IREC/27.10/294) for the study was granted from the Institutional Research Committee (IREC) of the Hubert Kairuki Memorial University (HKMU) in Dar es Salaam, Tanzania. Permission to conduct the study at the study sites was sought from the Municipal Director's offices of Ilala, Kinondoni and Temeke municipalities respectively. Hospital directors at Amana, Mwananyamala and Temeke also complemented institutional permits to collect data at the hospital premises. Mother of each studied neonates were approached and requested for a written informed consent to participate into the study on behalf of their newborns. Specifically, they had to make an informed decision for their babies' participations after being aware and fully informed about the study's goal, risks and benefits of participating into the study as well as voluntary nature of each participating child to withdraw/prevent from any study's data collection process without affecting care the child's receives

at the facility. For all babies that were found with sepsis, or who developed sepsis during follow-up period while at the hospital settings, they were treated free of charge following local hospitals' protocol for the management of neonatal sepsis.

Results.

We recruited (N = 427) and prospectively followed-up 9821 neonate-days at Amana, Mwananyamala and Temeke regional referral hospitals between 1st June 2023 to 31st August 2023. Neonates were prospectively matched for age at 1:1 (within +/- 2-days interval) unless a suitable matched-control was not present during the time of admission. Figure 1 below summarises the followed-up participants by groups:

Figure 1: Schema of followed-up study participants and their immediate cohort differences



Thus, we estimated the incidence rate of late-onset neonatal sepsis of 26.8 per 1000 live birth and a point prevalence of *late-onset neonatal sepsis* of around 61.6%. We could not evidently provide any instance of recurring neonatal sepsis nor did we found instances of *late-onset neonatal sepsis* for followed-up cases with other diagnoses. Besides, we obtained median *neonatal age on admission* and *respiratory rate on admission* to be 8 (IQR: 4-16) days and 64 (IQR: 55 - 74) b/min respectively. Otherwise, baseline comparative characteristics of maternal, neonatal and selected health-system related variables among newborns with presumptive symptoms/signs of *late-onset neonatal sepsis* (target group) versus newborns (≥ 3-days old) admitted due to other diagnoses (control group) are as summarized in table 1 below:

Table 1: Baseline maternal, neonatal and selected health system-based characteristics among followed-up newborns ≥ 3-days old admitted and followed-up at Amana, Mwananyamala and Temeke regional referral hospitals in Dar es Salaam, Tanzania between 1st June 2023 and 31st August 2023.

Variable	Late onset sepsis Frequency (%)	Control group Frequency (%)	Test Statistic	Measure of error in test statistic	P-value
Neonatal	**Baseline**	**Characteristics**			
Gender					
- Male	154 (62.9)	91 (37.1)	χ^2= 0.388	df = 1	.533
- Female	109 (59.9)	73 (40.1)			
Birthweight					
- < 2.5 kgs	41 (60.3)	27 (39.7)	χ^2=0.0576	df = 1	.81
- ≥ 2.5 kgs	222 (61.8)	137 (38.2)			
Birth order					
- Firstborns	32 (52.5)	29 (47.5)	χ^2= 2.51	df = 1	.11
- Others	231 (63.1)	135 (36.9)			
Central cyanosis					
Evident	**48 (82.8)**	**10 (17.2)**	**χ^2= 12.7**	**df = 1**	**<.001**
Non-evident	**215 (58.3)**	**154 (41.7)**			
	Median (IQR)	**Median (IQR)**			
Apgar score					
1st minute	**9 (9-10)**	**9 (8-10)**	**T-test = 4.5**	**df = 163**	**<.001**
5th minute	**10 (9-10)**	**7 (6-8)**	**T-test= 4.2**	**df = 163**	**<.001**
Temperature on admission					
Febrile (T ≥ 37.5◦C)	**38.6(37.9 – 39.2)**	**37.7 (37.5 – 37.9)**	**T-test = 14.1**	**df = 163**	**<.001**
Normothermic	36.7(36.4 – 37.0)	36.6 (36.0 – 37.0)	T-test = 0.9	df = 163	0.369
Hypothermic (T<36◦C)	**35.7 (35.7-35.9)**	**35.8 (35.8 – 35.9)**	**T-test = 8.8**	**df = 163**	**<.001**
Maternal	**Baseline**	**Characteristics**			
Modes of delivery					
-Caesarean section	54 (47.8)	59 (52.2)	χ^2= 0.404	df = 1	0.525
-SVD	161 (51.3)	153 (48.7)			
Number of antenatal care visits					
< 4	115 (59)	80 (41.0)	χ^2= 5.3	df = 2	0.07
4-6	134 (66.3)	68 (33.7)			
>6	14 (46.7)	16 (53.3)			

Gestational age at delivery					
<37 weeks	**26 (61.9)**	**16 (38.1)**	**χ^2= 6.7**	**df = 2**	**0.04**
37-41 weeks	**223 (60.3)**	**147 (39.7)**			
>41 weeks	**14 (93.3)**	**1 (6.7)**			
History of foul smelling liquor					
Evident	**23 (95.8)**	**1 (4.2)**	**χ^2=12.6**	**df = 1**	**<.001**
Non-evident	**240 (59.6)**	**163 (40.4)**			
Meconium-stained liquor					
Evident	**86 (78.9)**	**23 (21.1)**	**χ^2= 18.5**	**df = 1**	**<.001**
Non-evident	**177 (55.7)**	**141 (44.3)**			
Anemia during pregnancy					
Evident	**40 (42.6)**	**54 (57.4)**	**χ^2= 18.5**	**df = 1**	**<.001**
Non-evident	**223 (67)**	**110 (33)**			
Duration of labour	**20 (27)**	**54 (73)**	**χ^2= 4.9**	**df = 1**	**0.03**
< 12 hours	**144 (40.8)**	**209 (59.2)**			
≥ 12 hours					
Hospital	**System**	**Characteristics**			
Hand washing before touching the baby	**87 (32.2)**	**183 (67.8)**	**χ^2= 11.9**	**df = 1**	**<.001**
Observed	**77 (49)**	**80 (51)**			
Unobserved					
Place of delivery					
Home	12 (66.7)	6 (33.3)			
Dispensary	32 (69.6)	14 (30.4)	χ^2= 0.14	df = 2	0.93
Health centre	130 (66.7)	65 (33.3)			
Hospital					
Study site					**<.001**
Amana	**151 (84.4)**	**28 (15.6)**	**χ^2= 69.1**	**df = 2**	
Mwananyamala	**40 (40.4)**	**59 (59.6)**			
Temeke	**72 (48.3)**	**77 (51.7)**			

Note: *T-test used was independent T-test statistics (continuous variables) and χ^2 – test for independence (categorical variables)

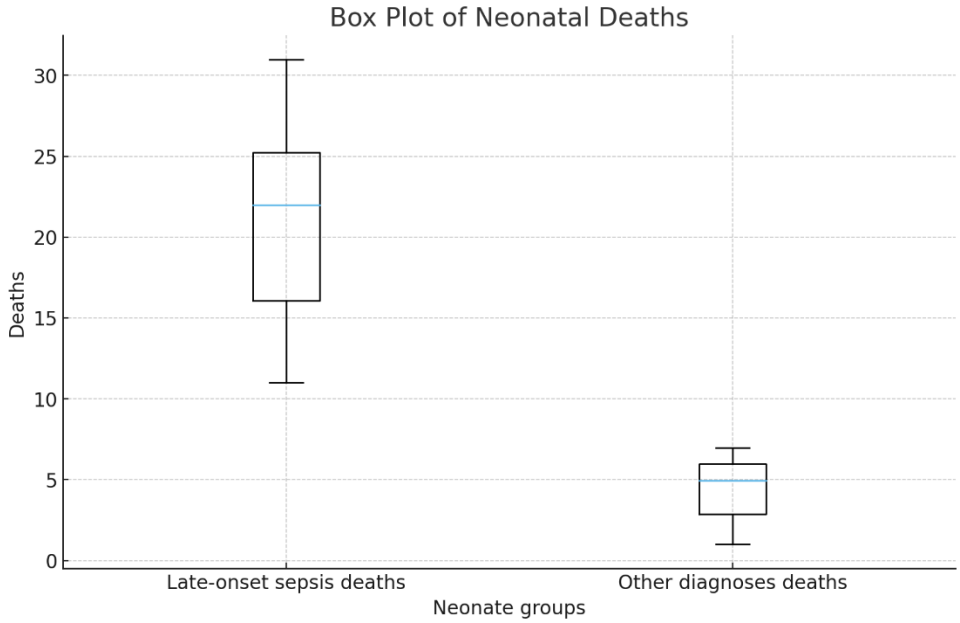
Besides, it was of interest to assess the immediate outcomes (specifically deaths) among studied neonates. Table 2 below compares immediate outcome statistics of neonates with presumptive symptoms/signs of late-onset neonatal sepsis (main group) versus neonates (≥ 3-days old) with other diagnoses.

Table 2: Comparative statistics of the association between neonates with presumptive symptoms/signs of late-onset neonatal sepsis (target group) versus neonates (≥ 3-days old) admitted due to other diagnoses (control group) and their immediate outcomes as observed Dar es Salaam public regional referral hospitals (June – August 2023)

Variable	Immediate Outcomes		Test	statistic	p-value
	Alive (n, %)	Dead (n, %)	χ^2-test*	Df	
Newborns with presumptive symptoms/signs of late-onset neonatal sepsis	**241 (91.6)**	**22 (8.4)**	**4.82**	**1**	**0.03**
Newborns (≥ 3-days) with other diagnoses [control group]	**159 (97)**	**5 (3)**			
Total	400	27			

Note: *χ^2-test of independence

Moreover, it was of interest to consider the immediate outcomes for followed-up cases, for both who survived or dead during the follow-up time. Figure 1 below displays the box plot of the estimates of deaths for both neonates with late-onset neonatal sepsis as well as those neonates (matched for age +/- 2days) admitted with other diagnoses during the same time.



Two-tailed Mann-Whitney U test = 398.7; p-value: <.001

Figure 2: Boxplot displaying comparative statistics of immediate outcomes (deaths) among neonates with presumptive symptoms/signs of late-onset neonatal sepsis (target group) versus neonates admitted due to other diagnoses (control group) during follow-up at Dar es Salaam public regional referral hospitals (June-August 2023)

Lastly, we also managed to assess for factors associated with presumptive symptoms/signs of late-onset neonatal sepsis in the studied newborns. We fitted a linear model to account for those factors after appropriate validation of model assumptions. Specifically, we fitted a multivariable binary logistic regression analysis model after validation of *linearity*, *homoscedasticity*, significant *multi-collinearity*, *autocorrelation*, *independence* and *normality* assumptions. Some factors (i.e. neonatal sex, Apgar scores at 1st and 5th minutes) failed in *linearity* and *homoscedasticity* assumptions, while others failed in autocorrelation (Apgar scores for both 1st and 5th minutes, birth order, neonatal temperature). For some others (i.e. maternal age) showed significant deviation in normality assumption. Thus, all those factors that deviated significantly during residual analyses were discarded in the final multivariable analysis done. In addition, we also fitted a model with effect modifiers (selected interactions with known clinical significance) vis-a-vis a model without interaction and compared their predictive powers. A model with interactions provided a better predictive powers with evidence of significant linear fitness (χ^2-goodness of fit test = 24.2, df = 17). Thus, summary statistics of the additive multivariable binary logistic regression model analysis is as shown in table 3 the underneath:

Table 3: Additive multivariable binary logistic regression model analysis for factors predictive of presumptive symptoms/signs of late-onset sepsis among neonates followed-up at Dar es Salaam public regional referral hospitals (June – August 2023).

Crude / Univariate analysis				Adjusted analysis		
Variable	**O.R.**	**95% C.I.**	**p-value**	**A.O.R.**	**95% C.I.**	**p-value**
Constant	**0.025**	**0.009 -0.391**	**<.001**	**.037**	**.008-.294**	**<.001**
Study site						
Amana	5.8	3.4 – 9.7	0.001	1.4	0.6 – 3.2	0.362
Mwananyamala	0.725	0.4 – 1.2	0.22	0.6	0.3 – 1.1	0.072
Temeke (Ref)	1			1		
Grunting						
Evident	**12.4**	**6.4 – 24.0**	**<.001**	**5.3**	**2.2 – 12.8**	**<.001**
Non-evident (Ref)	**1**			**1**		
Respiratory rate (b/min)						
<40 b/min	0.258	0.165 – 0.405	<.001	0.7	0.36 – 1.46	0.369
40 – 60 b/min	0.227	0.12 – 0.43	<.001	0.6	0.3 – 1.4	0.259
>60 b/min (ref)	1			1		
Lower chest in-drawing						
Evident	2.6	1.6 – 4.3	<.001	1.3	0.6 – 2.6	0.48
Non-evident (Ref)	1			1		
Central cyanosis						
Evident	3.4	1.7 – 7.0	<.001	0.9	0.4 – 2.3	0.846
Non-evident (Ref)	1			1		
Capillary refill						
Normal (≤2 seconds)	4.1	2.2 – 7.8	<.001	0.7	0.3 – 1.7	0.406
Abnormal (Ref)	1			1		
Place of delivery						
Home	1.8	0.6 – 4.95	0.273	1.2	0.3 – 4.1	0.785
Dispensary	2.0	1.0 – 4.1	0.047	1.0	0.4 – 2.5	0.994
Health centre	1.8	1.2 – 2.7	0.008	1.3	0.8 – 2.2	0.246
Hospital (Ref)	1			1		
Duration of labour						
≤ 12 hours	0.5	0.3 – 0.9	0.028	0.6	0.3 – 1.1	0.104
>12 hours (Ref)	1			1		
Anaemia in pregnancy						
Yes	0.4	0.2 – 0.6	<.001	0.7	0.4 – 1.2	0.177
No (Ref)	1			1		
Meconium stained liquor						
Yes	2.979	1.788 – 4.963	<.001	1.3	0.7 – 4.0	0.545
No (Ref)	1			1		
History of foul smelling liquor						
Yes	**15.6**	**2.1 – 116.8**	**0.007**	**10.4**	**1.2 – 92.7**	**0.036**
No (Ref)	**1**			**1**		
Gestational age at delivery						

Preterm (< 37 weeks)	9.2	1.2 – 70.9	0.033	5.3	0.6 – 48.6	0.142
Term (37 – 41 weeks)	1.1	0.6 – 2.1	0.837	0.9	0.4 – 2.0	0.766
≥42 weeks (Ref)	1			1		
Hospital the baby was born						
Amana	**0.2**	**0.1 – 0.7**	**<.001**	**0.5**	**0.2 – 0.7**	**0.01**
Mwananyamala	**1.9**	**0.9 – 3.0**	**0.127**	**1.4**	**0.9 – 1.9**	**0.053**
Temeke (Ref)	**1**			**1**		
Hospital site * hospital the baby was born						
Amana * Amana	**0.6**	**0.4 - 0.7**	**<.001**	**0.7**	**0.5 – 0.8**	**<.001**
Amana* Mwananyamala	**1.5**	**1.1 – 2.3**	**0.03**	**1.1**	**1.1 – 1.9**	**0.05**
Amana*Temeke	**1.1**	**0.9 – 11.2**	**0.88**	**2.7**	**0.6 – 15.2**	**0.23**
Mwananyamala*Mwananyamala	**2.6**	**1.8 – 3.2**	**<.001**	**1.4**	**1.2 – 1.9**	**0.004**
Mwananyamala*Amana	**0.9**	**0.6 – 3.4**	**0.812**	**1.1**	**0.7 – 11.5**	**0.9**
Mwananyamala * Temeke	**0.9**	**0.7 – 9.4**	**0.874**	**1.6**	**0.3 – 34.3**	**0.72**
Temeke*Amana	**0.8**	**0.7 – 1.3**	**0.158**	**3.6**	**0.8 – 9.0**	**0.157**
Temeke*Mwananyamala	**1.2**	**0.4 – 13.6**	**0.839**	**1.0**	**0.2 – 62.7**	**1.000**
Temeke*Temeke (Ref)	**1**			**1**		

Discussion

Our analysis revealed more than three-fifth of all neonates ≥ 3-days old admitted in the neonatal units at Dar es Salaam public regional referral hospitals to had *presumptive late-onset neonatal sepsis*. Our findings are consistent with similar findings reported at the same settings published before [24]. Evidently, Jabiri and colleagues published findings from two (Mwananyamala and Temeke) of the current three studied hospitals revealed prevalence of *late-onset neonatal sepsis* to had been about 69.3% back in 2015 [24]. However, whereas our analysis was powered to deliver the incidence rate estimate of presumptive diagnosis of late-onset neonatal sepsis, findings from Jabiri and others, and even other findings from Tanzania before; were all deficient to give such an estimate [15-17, 24]. Moreover, those studies assumed neonates as a generalised group. The fact that neonatologists and child health specialists have made demarcation between early and late-onset neonatal sepsis, makes it highly likely that findings from Jabir and colleagues had significantly under-estimated *late-onset neonatal sepsis*. Given the accumulated evidence for significant amount of late-onset infections in newborns to be secondary to either hospital environmental or community-acquired pathogens [10, 11, 15-22, 25]; points to probable inadequate sanitary control measures. Thus, it is clear that appropriate intervention strategies on a timely basis to be a significant solution towards reduction/elimination of *late-onset neonatal sepsis* in our settings.

We also provided statistical probable evidence for more deaths among neonates with *presumptive late-onset neonatal sepsis* compared to their controls matched for age at the study settings. Specifically, we have been able to estimate that on average neonates with *late-onset sepsis* were almost three times more likely to die compared to similar admitted neonates (matched for age) with other diagnoses. Even though confounding could not be completely ruled-out in findings; estimates of outcomes (especially deaths) among tested groups were considered statistically significant. In fact, previous studies have shed light on the

pathophysiological mechanisms behind increased chances to mortality due to late-onset sepsis among early neonatal death survivors to include Gram-negative organisms, especially *Pseudomonas aureginosa* (excess mortality rate: 19%-36%) [25-28], usage of central venous catheters [29] and even unknown intra-hospital factors [25]. Otherwise, our findings are consistent with others reported before, both from Tanzania [15-17] and overseas [10, 11, 18-22].

We also revealed the factors of neonatal grunting, maternal reported history of foul-smelling liquor, hospital of child's birth as well as the effect modification for the combined factors of hospital site and hospital of child's birth, to be statistically significant associated with probability of presumptive diagnosis of *late-onset neonatal sepsis* in this study population. Specifically, given our fitted linear multivariable model, neonates who presented with grunting had more than 5-folds increased chances of presenting with *presumptive late-onset neonatal sepsis* compared with neonates without grunting, all other factors in check. Moreover, neonates whose mothers had reported history of foul smelling liquor during labour were reported to have up to 10-folds statistically significant increased chances of being found with late-onset sepsis compared to those whose mothers did not have a reported history of foul smelling liquor during labour. Interestingly, the statistical interaction between the factors named *hospital of child birth* and *hospital site of admission* also revealed statistically significant association to the probability of *presumptive late-onset neonatal sepsis*. Grunting in newborns is a marker of respiratory distress, especially if associated with group B-streptococcal infections [30]. Previous report from India revealed grunting as a sign included as part of the clinical criteria to identify sepsis to had a negative predictive value of 100%, sensitivity of 100% and specificity of 92% [31].

Hospital-related factors displayed even more interesting patterns upon further scrutiny. Specifically, they revealed differential associated/protective risks by virtue of their direction of risks. Neonates who were born at Amana hospital and later on admitted at Amana hospital were found to have up to 30% less likelihood of presumptive diagnosis of late-onset neonatal sepsis compared to neonates born at Temeke hospital and admitted at Temeke hospital, all other factors in check. At the same time, newborns born at Mwananyamala hospital and later-on admitted at Mwananyamala hospital had up to 44% increased chances of presumptive diagnosis of late-onset neonatal sepsis compared to those from Temeke hospital, all other factors in check. The fact that all the three studied hospital facilities are in the same hierarchy and serviced by the central government in Tanzania makes the estimates of risks displayed extremely interesting. We hypothesized *the latent factor(s)* responsible for such a pattern to be directly related to individual hospital factors. It is an important area of future exploration by audit committees/scientists with interest in infectious diseases for future research.

This study had several strengths up and above others published on the same topic to date for several reasons. First, we conceived it using prospective cohort design. Thus, we could in principle estimate even the incidence rate. Likewise, we managed to match and later via a multivariable binary logistic regression model account for potential confounding. Moreover, our fitted multivariable model was an additive one, and hence we were able to pick and linearly characterize even *effect modifiers* (statistical interactions) that were associated with what we characterized as probability of '*presumptive late-onset neonatal sepsis*'. In so doing, we do believe our fitted model could be used for both predictive, descriptive and even controlling/optimisation

purposes, with ease to busy practitioners, scientists with interests in either decision sciences or predictive analyses as well as decision makers with tighter regulatory and control capabilities. Moreover, and this comes as the strongest finding in our analysis, is the fact that part of what we found to be associated with presumptive late-onset neonatal sepsis (e.g. *maternal history of fouls smelling liquor during labour*) to be evidently attributed to early neonatal sepsis. Earlier reports documented on this pattern and gave rise to philosophical debate about whether the dichotomization of neonatal sepsis on the basis of environmental milieu is objective from logical viewpoint [7, 9, 10]. Thus, our findings may be used as among potential evidence against the utility of the current dichotomy, and further streamline more analytical research on the nosology and clinical frameworks of newborn infections in general.

We wish also to caution about some few limitations of our study design and analysis. First, as it may be obvious, we limited our analysis and even reporting to presumptive symptoms and signs of what is termed as *late-onset sepsis*. The decision to do so, though attractive to child health doctors working in developing nations like Tanzania, must be balanced with the utility of the gold standard reporting of late-onset sepsis using microbial isolates and even anti-microbial susceptibility test results. This comes handy even on the grounds of more recent developments towards the proposed shift of gold standard methods for microbial isolates from laboratory culture to molecular and gene-based technologies [32-34] Moreover, we limited our analysis to the fitted multivariable linear model. We wish to warrant readers here, our fitted model, as interesting and parsimonious as it seems, was far from perfect. In fact, most of the otherwise important variables were likely *knocked-out* probably on the basis of failed test assumptions for linearity, even when clinically predictive. To our reasoning, we considered simplicity and prescription to perfection!

Otherwise, on a distant but equally important aspect, our analysis has several important messages to global health initiatives, philosophy of science (especially the sub-field of study of medical science known as *nosology*), statistics associated with morbidity and mortality in general. First, it was obvious that the philosophical debate against the widespread application for the definition of neonatal sepsis on the basis of age of the neonate to be probably valid. We could only pick grunting (a clinical sign of respiratory distress associated with group B streptococci infection) as a sign of late-onset neonatal sepsis. The same sign is a sequelae of organisms that are widely associated with early-onset sepsis. Thus a total avenue of confusion!

Moreover, it was obvious in our analysis, that despite efforts and resources utilized for controlling infections in newborns, the results are not favourable. The fact that the burden of late-onset neonatal sepsis is still unacceptably high in Dar es Salaam public hospitals, further frustrates the imbalance between resources and results for health. Besides, there are several studies in the same settings that suggest majority of children under-fives in Tanzania to be in ill-state, especially displaying antecedent cues associated with infections [35-40]. It is not clear at present, whether those antecedents are causally related to newer infections born outside neonatal era, or simply a long-term sequela of what started in the neonatal era. Part of the challenges being absence of reliable and valid means to quantify healthcare parameters not only in neonatology [41-43] but throughout the entire human lifespan [44-46]. We have just established local initiative for global health solution across the entire human lifespan both in Tanzania and the globe at large [45, 47-51].

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Conflict of Interest statement

All authors declare no conflict of interest in design, analysis, reporting and preparation of this study findings

Authors' contributions:

CCG - Study conception, design, methodology, funding acquisition, investigation, data collection, study administration, software, data analysis, writing original draft, reviewing and editing the final draft.

FSK - Study conception, design, methodology, investigation, supervision, visualization, data analysis, reviewing and editing the final draft.

MRF – Study conception, design, methodology, investigation, supervision, visualization, data analysis, reviewing and editing the final draft.

GFM - Study conception, design, methodology, visualization, validation, data analysis, reviewing and editing the final draft.

KML - Study conception, design, methodology, supervision, visualization, validation, data analysis, writing original draft, reviewing and editing the final draft.

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