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## Referral pattern and outcomes of neonates from secondary care setting of Aga Khan University hospital to tertiary care centers in Pakistan

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## Referral pattern and outcomes of neonates from secondary care setting of Aga Khan University Hospital to tertiary care centers in Pakistan

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### Abstract

**Objective:** To determine the reasons of neonatal referrals from secondary-care to tertiary-care setting, and to assess neonatal outcomes for the referred cases.

**Method:** The retrospective study was conducted at the Aga Khan University Hospital, Karachi, and comprised data from July 2015 to June 2019 Related to all neonates born after 32 weeks of gestation at the satellite secondary-care centres in Kharadar, Garden and Karimabad who had been referred to the main tertiary care hospital. The reason for referral, need of mechanical ventilation, referral place and neonatal outcome were noted. Data was analysed using SPSS 22.

**Results:** Of the 348 cases, 211(60.6%) were boys. The overall mean gestational age was 36.42±2.61 weeks and the mean birth weight was 2.54±0.67 kg. The outcome was neonatal mortality in 42(12%) cases. Of the remaining 306(88%) cases, 284(92.81%) were discharged from the hospital and 22(7.18%) left against medical advice. Overall, mechanical ventilation was needed in 63(18.1%) patients. There was a significant association of mechanical ventilation with low Appearance, Pulse, Grimace, Activity, and Respiration score at 1 and 5 minutes ( $p<0.001$ ), shorter duration of stay ( $p=0.007$ ), and aggressive resuscitation requirement at birth ( $p<0.001$ ).

**Conclusion:** The most common reasons for referral of newborns to tertiary care hospital were respiratory diseases requiring respiratory support and surgical intervention.

**Keywords:** Neonates, Outcomes, Referral pattern, Mortality. (JPMA 71: 1432; 2021)

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### Introduction

Neonatal period is often the most vulnerable period of human life, particularly in underdeveloped countries. It accounts for very high morbidity and mortality most of which are preventable.<sup>1</sup> A global survey in 2015 reported that 2.7 million children died in the first month of life.<sup>2</sup>

Sepsis (45.4%), birth asphyxia (23.9%), respiratory distress syndrome (13.3%) and congenital abnormalities (4.9%) are among the most common causes of neonatal death in Pakistan.<sup>3</sup> It is global issue and the same trend is observed in Pakistan. The pattern of neonatal disease changes from time to time and varies with geographical location.<sup>4</sup> A recent systematic analysis reported considerable decline in neonatal mortality in the past decades. However, global trend revealed that still remarkable improvement is required in sub-Saharan Africa and south Asia to achieve sustainable developmental goal (SDG) target level by 2030.<sup>5</sup>

Timely referral of high-risk pregnancies and newborn babies requiring specific therapies at tertiary care centres can play a vital role in reducing neonatal morbidity and mortality.<sup>6</sup> Referral is a process of coordinated actions

involving a healthcare seeker to reach a high-level care within a narrow window of time.<sup>7</sup>

Ten countries, including India, China, Pakistan and Nigeria, account for 75% of all neonatal deaths.<sup>8</sup> To plan a strategy for reduction in neonatal mortality (NNM) rate and prioritisation of resources, it is important to know factors contributing to neonatal deaths. Referral of critical patients from one hospital to another also causes time-waste in critical patients, especially neonates. Non-availability of required healthcare facility, like ventilator, surgical intervention, premature care and even delay in the arrangement of a bed, means sub-optimal early management of the neonates. Increased investment in health by governments is necessary to tackle the factors predisposing the unacceptably high neonatal mortality rates in developing regions.<sup>9,10</sup>

The current study was planned to assess the referral pattern of high-risk neonates, and to explore the predictors of mortality of neonates referred to a tertiary care hospital from a secondary-care setting.

### Materials and Methods

The retrospective study was conducted at the Aga Khan University Hospital (AKUH), Karachi, and its satellite neonatal unit Level II nursery of secondary-care hospitals at Kharadar, Karimabad and Garden, and comprised data

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from July 2015 to June 2019.

After approval from the institutional ethics review committee, data was retrieved related to babies born after 32-week gestation at one of the secondary-care facilities from where they were referred to the tertiary-care hospital. Data related to neonates born outside AKUH was excluded.

Medical records were retrieved from the Hospital Information Management System (HIMS) using the International Classification of Diseases (ICD) discharge codes.<sup>11</sup> Data was taken down on a predesigned proforma, and included basic demographic and clinical information of the neonates, such as gestational age at birth, birth weight, gender, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score, date of delivery, mode of delivery, working diagnosis, reason of referral, date of referral, time of referral, place of referral, reason for non-referral to AKUH, and neonatal outcomes. Moreover, maternal information, like pregnancy-induced medical disorders and obstetrical complications during current pregnancy, were also noted. Outcome of neonates referred outside AKUH was recorded from hospital monthly mortality and morbidity (M&M) meeting data.

Gestational age, recorded as completed weeks, was calculated from maternal last menstrual period (LMP) and was categorised as preterm <37 weeks and term as 37 or more weeks. As per routine practice, weight was measured by staff nurse in the labour room or operation theatre (OT) by using standardised equipment. Weight was measured without clothes using standard weighing balance in kilogram (kg). The calibration of the weighing scale was checked regularly before each measurement in order to avoid an error. Pregnancy-induced medical disorders and obstetrical complications, like placenta previa, abruptio placentae, anaemia, pregnancy-induced hypertension (PIH) and gestational diabetes mellitus

(GDM), and whether the mother had received antenatal steroid (in-utero dexamethasone [DEXA]) were also noted. APGAR score had been documented at 1 and 5 minutes after delivery. Working diagnosis was categorised as respiratory diseases, cardiac diseases, infectious, metabolic, diseases of digestive, renal and endocrine. Reason of referral included surgical intervention, respiratory support, premature care and other reasons, like perinatal asphyxia, thrombocytopenia, suspected congenital heart disease (CHD), congenital anomalies, very low birth weight (VLBW). Place of referral, whether AKUH or other tertiary-care hospital, and reason of referral to other tertiary-care hospital, like unavailability of bed at AKUH or financial issues, were also documented. Neonatal outcome included patient expired, left against medical advice (LAMA) from the referral place and discharged home in a stable condition. The outcome variable was dichotomised by merging discharges and LAMA into single category and expired/death as the second category.

Data were analysed using SPSS 22. Descriptive analysis was carried out to calculate frequencies and percentages of categorical variables, and means along with standard deviations for continuous variables. Univariate and multivariate logistic regression analysis was performed to find out the putative risk factors of poor outcome (death) among the referred cases. Unadjusted and adjusted odds ratios (OR/AOR) with 95% confidence interval (CI) were also measured. All the variables were assessed in univariate analysis, and those with  $p < 0.25$  and biologically plausible regardless of  $p$ -value, were assessed in multivariate models. Variables in the final model were retained based on contribution of variables in the model assessed by -2 log likelihood ratios (LLRs).

## Results

Of the 348 cases, 211 (60.6%) were boys. The overall mean

**Table-1:** Comparison of referral reasons with baseline characteristics of the patients (n=348).

Variables	Reasons of Referral				p-value
	Respiratory Support	Care of Prematurity	Surgical Intervention	Others	
	226 (64.94%) Mean $\pm$ SD	6 (1.72%) Mean $\pm$ SD	31 (8.91%) Mean $\pm$ SD	85 (24.43%) Mean $\pm$ SD	
Gestational Age, weeks	35.97 $\pm$ 2.81	36.83 $\pm$ 1.47	36.96 $\pm$ 2.28	37.35 $\pm$ 1.86	<0.001
Birth Weight, Kg	2.48 $\pm$ 0.69 n (%)	1.44 $\pm$ 0.27 n (%)	2.78 $\pm$ 0.47 n (%)	2.66 $\pm$ 0.59 n (%)	<0.001
<b>In utero Dexamethasone (DEXA) received</b>					
Yes	60 (82.2)	2 (2.7)	4 (5.5)	7 (9.6)	0.002
No	166 (60.4)	4 (1.5)	27 (9.8)	78 (28.4)	
<b>Diagnosis</b>					
Respiratory related causes	170 (85.4)	0 (0)	2 (1.0)	27 (13.6)	<0.001
Non-respiratory related causes	56 (37.6)	6 (4)	29 (19.5)	58 (38.9)	

The following variables were found non-significant: gender ( $p=0.576$ ), short duration of stay at secondary care ( $p=0.145$ ), Appearance, Pulse, Grimace, Activity, and Respiration (APGAR\_ score at 1 min ( $p=0.333$ ), APGAR score at 5 min ( $p=0.145$ ), anaemia ( $p=0.936$ ), antenatal scan ( $p=0.536$ ), premature rupture of membrane ( $p=0.754$ ), comorbidity ( $p=0.976$ ), mode of delivery ( $p=0.519$ ), resuscitation required ( $p=0.359$ ), others (perinatal asphyxia, thrombocytopenia, suspected congenital heart disease (CHD), congenital anomalies, very low birth weight.)

**Table-2:** Comparison of mechanical ventilation with baseline characteristics (n=221).

Variables	Mechanical Ventilation		p-value
	Yes 63 (28.51%) Mean $\pm$ SD	No 158 (71.49%) Mean $\pm$ SD	
Duration of stay at secondary care(days)	1.82 $\pm$ 0.95	2.39 $\pm$ 1.53	0.007
<b>Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at 1min</b>			
<7	21 (50)	21 (50)	<0.001
$\geq$ 7	42 (23.5)	137 (76.5)	
<b>APGAR score at 5 mins</b>			
<7	18 (81.8)	4 (18.2)	<0.001
$\geq$ 7	45 (22.6)	154 (77.4)	
<b>Resuscitation required</b>			
Yes	21 (51.2)	20 (48.8)	<0.001
No	42 (23.3)	138 (76.7)	

Following variables were found non-significant: gestational age (p=0.801), birth weight (p=0.236), gender (p=0.746), mode of delivery (p=0.277), in utero dexamethasone (DEXA) received (p=0.084), comorbidity (p=0.480), premature rupture of membrane (p=0.852), diagnosis (p=0.081).

**Table-3:** Comparison of mortality with baseline characteristics (n=348).

Variables	Mortality		p-value
	Yes 42 (12.07%) Mean $\pm$ SD	No 306 (87.93%) Mean $\pm$ SD	
Gestational Age, weeks	35.50 $\pm$ 2.56	36.54 $\pm$ 2.59	0.015
Birth Weight, Kg	2.22 $\pm$ 0.74	2.58 $\pm$ 0.65	<0.001
Duration of stay at secondary care ( days)	1.85 $\pm$ 1.39	2.26 $\pm$ 1.34	<0.001
<b>Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at 5 mins</b>			
<7	12 (31.6)	26 (68.4)	<0.001
$\geq$ 7	30 (90.3)	280 (90.3)	
<b>Resuscitation required</b>			
Yes	17 (23.6)	55 (76.4)	<0.001
No	25 (9.1)	251 (90.9)	
<b>Diagnosis</b>			
Respiratory related cause	35 (17.6)	164 (82.4)	<0.001
Non-respiratory related cause	7 (4.7)	142 (95.3)	
<b>Mechanical Ventilation Required</b>			
Yes	25 (39.7)	38 (60.3)	<0.001
No	6 (3.8)	152 (96.2)	
<b>Referral Place</b>			
Aga Khan University (AKU)	8 (5.4)	139 (94.6)	0.001
Outside AKU	32 (16.9)	157 (83.1)	
<b>Reason for Referral</b>			
Respiratory Support	36 (15.9)	190 (84.1)	0.014
Care of Prematurity	1 (16.7)	5 (83.3)	
Surgical Intervention	0 (0)	31 (100)	
Others (perinatal asphyxia, thrombocytopenia, suspected congenital heart disease (CHD), congenital anomalies, very low birth weight).	5 (5.9)	80 (94.1)	

Following variables were found non-significant: gender (p=0.406), mode of delivery (p=0.721), in utero DEXA received (p=0.376), comorbidity (p=0.522), antenatal scan (p=0.080), premature rupture of membrane (p=0.969), diagnosis (p=0.191).

gestational age was 36.42 $\pm$ 2.61 weeks and the mean birth weight was 2.54 $\pm$ 0.67 kg. Resuscitation was required in 72(20.7%) cases; 165(47.4%) of the deliveries were emergency lower segment caesarean section (EMLSCS);

73(21%) received in utero DEXA; 43(12.4%) mothers had GDM; 27(7.8%) had PIH; 6(1.7%) had UTI; 17(4.9%) had premature rupture of the membranes (PROM); and 69(19.8%) had abnormal antenatal scan.

**Table-4:** Regression analysis of variables associated with mortality (n=348).

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p-value	AOR (95% CI)	p-value
Gestational Age, weeks	0.87 (0.78-0.97)	0.017	0.89 (0.78-1.01)	0.080
Birth Weight, Kg	0.43 (0.26-0.72)	0.001	0.50 (0.27-0.90)	0.021
Duration of stay, days	0.75 (0.56-1.02)	0.069	-	
<b>Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at 5min</b>				
<7	4.31 (1.97-9.40)	<0.001	4.84 (1.24-18.89)	0.023
≥7	Ref	Ref		
<b>Resuscitation required</b>				
Yes	3.10 (1.57-6.14)	0.001	1.69 (0.56-5.09)	0.348
No	Ref	Ref		
<b>Diagnosis</b>				
Respiratory related cause	4.32 (1.87-10.04)	0.001	3.33 (1.34-8.26)	0.009
Non-respiratory related cause	Ref	Ref		
<b>Referral Place</b>				
Aga Khan University (AKU)	0.28 (0.13-0.63)	0.002	0.28 (0.12-0.68)	0.005
Outside AKU	Ref	Ref		

OR: Odds ratio; AOR: Adjusted odds ratio.

All variables with p-value <0.25 included in multivariate analysis.

Respiratory diseases was found to be the main cause of admission and later referral among the neonates 199(57.2%); 226(64.9%) needed respiratory support; 31(8.9%) needed surgical intervention; 6(1.7%) needed premature care; and 85(24.4%) had miscellaneous reasons for being referred. Significant association of reasons of referral was found with gestational age, birth weight, diagnosis and in utero DEXA injection ( $p<0.05$ ) (Table-1).

The referral place of 189(56.3%) patients was outside AKUH. A significant association of mechanical ventilation was found with neonates having low APGAR score at 1 and 5 minutes, short duration of stay at secondary-care facility and aggressive resuscitation requirement ( $p<0.05$ ) (Table-2).

The outcome was neonatal mortality in 42(12%) cases. Of the remaining 306(88%) cases, 284(92.81%) were discharged from the hospital and 22(7.18%) left against medical advice. A significant association of mortality was observed with gestational age, birth weight, APGAR score at 5 minutes, duration of stay, diagnosis, resuscitation requirement, mechanical ventilation requirement, referral place and reasons of referral ( $p<0.05$ ) (Table-3).

Univariate analysis revealed that gestational age, birth weight, and AKUH as the referral place significantly reduced the odds of mortality, whereas neonates with APGAR score <7 at 5 minutes, requirement of resuscitation, and diagnosis had significantly higher odds of mortality ( $p<0.05$ ). On multivariate analysis, after adjustments, similar mortality trends were observed, with

APGAR score <7 at 5 minutes and diagnosis being the only variables found significantly more likely to have mortality, whereas birth weight and referral place being AKUH were the only variables found significantly less likely to have mortality (Table-4).

## Discussion

While there are several neonatal conditions that contribute to the global burden of neonatal referrals, premature birth, birth asphyxia and neonatal infections are among the most common.<sup>12</sup> Of the total neonates enrolled in the current study, males were predominantly more. This is consistent with earlier findings.<sup>13-16</sup> This variance in gender of neonates has been explained as differential survival prospects which may lead to a natural selection response.<sup>17</sup>

The average gestational age in the current study was 36 weeks, with six cases of prematurity. Moreover, the proportion of preterm admission was 1.7%, which was considerably low compared to previous studies findings that ranged 25-50%.<sup>14-18</sup> This difference may be caused by multiple reasons, such as cost as a barrier to entry, and requires further evaluation. There is a wide variety of factors associated with prematurity, but financial constraints, maternal infection, malnourishment and low haemoglobin (Hb) level are some of the factors reported previously.<sup>19-22</sup> Maternal comorbidity was found in one-fifth of the mothers, with GDM (12.4%), PIH (7.8%) and urinary tract infections (UTI) (1.7%) being the most common.

The most common reasons of referral identified were the need for respiratory support and surgical intervention. However, these statistics are notably high compared to previous studies.<sup>14,15</sup> A local study reported 7.8% occurrence of respiratory distress and need for subsequent support.<sup>13</sup> This increase can be attributed to the fact that AKUH is one of the largest tertiary-care hospitals of Karachi with more resources than secondary-care setups, and thus receives a large number of cases due to its resource-rich setup. The number of referrals for surgical intervention can also be explained similarly. A study from Uganda found that only a negligible fraction of the population needing neonatal surgery as most institutions may lack the infrastructure and the expertise required.<sup>15</sup>

In our data set, a significant association of referral to tertiary centres was found with gestational age, birth weight and mode of delivery. The risk of complications and mortality increases with low gestational age and low birth weight, which may often increase the chances of emergency caesarean procedures,<sup>21</sup> and may subsequently sway a need to refer the neonate to a tertiary-care facility.<sup>13</sup> Mechanical ventilation was required in 18.1% cases and a significant association of mechanical ventilation was observed with low APGAR score at 1 and 5 mins, and referral to tertiary hospital.

In the current study, neonatal mortality was 12% and mortality was less in neonates referred to AKUH compared to those who were referred outside AKUH. This finding somewhat matched with findings reported from Nigeria (15.7%) and South Africa (13.8%), but is lower in comparison with Ethiopia (23.2%) and Bangladesh (43.2%). On the flip side, lower mortalities of 1.4% and 6.2% have also been reported from Nepal and Pakistan.<sup>14,16,22-24</sup> This variance in neonatal mortality may be due to by the related factors studied in each individual setting as well as the standard of care provided by AKUH and timely referral from secondary-care facilities.

The current study has limitations, as, due to its retrospective nature, certain important predictor variables which can affect neonatal outcomes, such as maternal comorbidities and antenatal counselling of mothers, were not included. Despite the limitation, the study has reported data from one of the largest private hospitals in the country. Further longitudinal analytical studies are recommended with larger sample sizes to validate the findings of the current study.

## Conclusion

The most common reasons of referral to tertiary-care centre was respiratory diseases for which respiratory support and

surgical intervention were provided. Mortality noted was less in neonates referred to the AKUH compared to those who were referred elsewhere. Besides, timely referral from secondary-care to tertiary-care facility was also found to be an important factor in improving neonatal outcomes.

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**Conflict of Interest:** None.

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