Risk factors of stillbirth among mothers delivered in public hospitals of Central Zone, Tigray, Ethiopia

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Abstract

Background: Stillbirth is a death before the complete expulsion or extraction from the mother. The burden is severe and high in developing countries. Risk factors for stillbirth are not yet studied in Ethiopia.

Objective: To identify risk factors of stillbirth among mothers delivered in public hospitals of Central Zone Tigray, Ethiopia **Methods**: A case-control study design was used. Data collection period was from January to April 2018. Study subjects 63 cases and 252 controls were selected using systematic random sampling technique from respective hospitals. The interviewer-administered questionnaire, observational, and chart analysis were used to collect the data. A binary logistic regression model was employed. Results were presented at significance level P-value <0.05.

Results: Maternal hypertension [AOR=12.83; 95% CI 3.38, 48.83], low birth weight [AOR=5.6; 95% CI 2.39, 13.38], pre-term [AOR=2.6;95%CI 1.12,6.16], alcohol intake [AOR=7.56; 95% CI 1.68, 34.04], polyhydramnios [AOR=13.43; 95% CI 3.63, 49.67], and meconium stained amniotic fluid [AOR=7.88; 95% CI 1.73, 8.18] were risk factors of stillbirth.

Conclusion: The risk of stillbirth is increased with increasing maternal complication like maternal hypertension, alcohol consumption, polyhydramnios, and meconium-stained amniotic fluid. The occurrence of preterm and low birth weight of the fetus had an effect on the risk of stillbirth.

Keywords: Stillbirth, Risk Factors, Neonates, Central Zone, Tigray, Ethiopia.

DOI: https://dx.doi.org/10.4314/ahs.v19i2.16

Cite as: Tasew H, Zemicheal M, Teklay G, Mariye T. Risk factors of stillbirth among mothers delivered in public hospitals of central zone, Tigray, Ethiopia. Afri Health Sci.2019;19(2): 1930-1937. https://dx.doi.org/10.4314/ahs.v19i2.16

Introduction

Stillbirth is defined as a fetus born dead. Stillbirth is death after 20 weeks of pregnancy in developed countries and after 28 weeks of pregnancy in developing countries, be-

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Hagos Tasew, School of Nursing, College of Health Science and Comprehensive Specialized Hospital, Aksum University, Tigray, Ethiopia. Email: tasewh2@gmail.com fore the complete expulsion or extraction from its mother of a product of conception, which is indicated by the fact that after such separation, the fetus does not show any evidence of life^{1,2}.

Globally 3.3 million stillbirths occur each year, accounting for over half of all perinatal deaths^{3,4}. Most of these deaths take place in resource-limited countries. The poorest countries of the world have the highest incidences with two regions, sub-Saharan Africa and South Asia, together accounting for nearly 70% of worldwide stillbirths³. In developed countries, stillbirth rates are as low as 6 per 1000 live births, whereas in limited resources countries they can be as high as 26 per 1000 live births⁵.

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The high rates of stillbirth result from poor maternal health, inadequate antenatal and post-partum care. Poor health services was unquestionably a risk factor of stillbirth, but there is increasing concern that high stillbirth rates in many regions are also being driven by less apparent, possibly preventable factors⁶. Thus, stillbirth is a public health as well as a development problem on the continent, as in other low-income regions. Yet the sorrow endured by parents who have had experience a stillbirth in these settings residues indescribable. Stillbirth in many countries leaves parents with many challenges, such as illness, woe, wretchedness, and coping with community perceptions^{4,7}.

Largely, there is an overwhelming burden of the stillbirths, a proportion of which has no clinical elucidation or certain cause in spite of a complete evaluation. The potential risk factors for stillbirths include maternal factors consisting of demographics, environmental, nutritional, and lifestyle factors, maternal infections and non-communicable diseases, and fetal factors, which are considered modifiable risk factors⁸. The fact that most of the stillbirths were fresh suggests that higher quality intrapartum care could reduce stillbirth rates⁹.

There are a few kinds of literature on stillbirths in developed countries, but there are too few numbers of articles keen to stillbirths in developing countries. It is important to conduct further studies to investigate risk factors of stillbirth to determine which stillbirths are preventable so that targeted interventions can be developed and tailored for limited resource settings⁹. Consequently, this article has tried to investigate the risk factors of stillbirth, which may highlight potential methods of prevention.

Methods and materials Study area and period

The study was conducted in public Hospitals of Central Zone, which is one of the seven administrative zones of Tigray. Based on the census conducted by the Central Statistical Agency of Ethiopia CSA, the Zone has a total population of 1,245,824, of whom 613,797 are men and 632,027 women; 176,453 or 14.16% are urban inhabitants¹⁰. In the Central Zone, there are four public hospitals Aksum University referral hospital, St. Marry hospital, Adwa hospital, and Abyiadi hospital. Axum town is the capital city of the Central Zone and has two public hospitals. St. Marry hospital is one of earliest district hospital found in the town and with newly innovated referral hospital. The other two hospitals of the zone found in the Adwa and Abyiadi towns.

Data collection period was from January to April 2018.

Study design

A hospital-based unmatched case-control study design was employed.

Source population

The source population was all mothers came for delivery in public hospitals.

Study population

For cases: Mothers with their newborns who diagnosis as stillbirth.

For controls

Mothers with live birth.

Sample size calculation

Sample size of the study was calculated using EPI Info statistical software version 7.1.1 with the following parameters for unmatched case control study. Confidence level = 95%; Power = 80%; Odds ratio = 2.33; Case to control ratio = 1: 4: Proportion of controls with exposure 29.4 %¹¹; Proportion of cases with exposure = 49.2 %¹¹ the total sample size for cases=63; sample size for controls =252 the overall sample size was = 315.

Sampling technique

Systematic random sampling technique was used to select the study subjects from four public hospitals Aksum University referral hospital, St. Marry hospital, Adwa hospital, and Abyiadi hospital with every two-study subjects for both cases and controls.

Study variables Dependent variable •Stillbirth

•Stillbirth

Independent variables

Antepartum factors, for example age of mother, hypertension, pre-eclampsia, antepartum hemorrhage, drug and smoking history, type of pregnancy, history of diabetes, anemia, any previous history of birth asphyxia, etc. Intra-partum factors included meconium stained, presentation of the fetus, mode of delivery, type of assisted vaginal delivery, history of prolonged labor, place of delivery, any emergency complication of the mother, etc. Fetal factors fetal condition included diagnosed during pregnancy, gestational age at birth, history of breathing, birth weight, sex, etc.

Operational definitions

The cases of the study were determined with clinical features. Assess, look of breathing on following signs Is baby not breathing? Or if the baby has not any sign of life, patients were diagnosed as stillbirth or case of the study¹².

Alcohol intake: alcohol consumption intake was considered as excessive intake if it is either more than 2 bottles of beer or 3 ounces of liquor for men, 1 bottle of beer or 1.5 ounces of liquor for women per day.

Data collection tool and procedure

The questionnaire was initially prepared in English and then translated into Tigrigna. Data was collected using interviewer-administered structured questionnaire adapted^{8,12,13}, observational and chart analysis. The questioner reliability was checked using Cronbach's alpha with a value of 0.79. Four BSc nurses' data collectors with previous experience of data collection were recruited to run the data collection procedure. Continuous follow-up and supervisors and principal investigator throughout the data collection period made supervision.

Data quality control

Quality of the data was certain with appropriately designed data collection tools. The data collectors and the supervisor were given training for three days on procedures, techniques, and ways of collecting the data. Five percent pretest was done at Shul hospital to check uniformity of the tool. The principal investigator and co-investigators appraised and checked for completeness of the data weekly.

Data processing and analysis

Data was entered and prepared using Epi info version 7.1.1. Data were investigated using SPSS version 22.0 and variables, which showed statistical significance during bivariate analysis at p-value ≤ 0.25 , moved in into multivariable logistic regression. Lastly, the data was presented and inferred at the thresholdset at 5%. All assumptions of binary logistic regression were checked accordingly.

Results

Socio-demographic characteristics of study participants

In this study, a total of 63 partakers who had stillbirths with their index mothers and 252 participants who had live births (controls), with their index mothers were encompassed making a response rate of 100%. The mean age of mothers was 27.27 SD \pm 5.82. Thirty-eight 60.3 % of cases and 97 (38.5%) controls were living in pastoral areas. Regarding marital status, 51 (81.0 %) cases and 236 (93.7%) of controls were wedded. Thirty-nine (61.9 %) of cases and 118 (46.8 %) of controls were housewives and 20 (31.7 %) cases and 38 (15.1 %) of controls were not able to read and write Table 1.

 Table 1: Distribution of socio-demographic characteristics of cases and controls attending public hospitals of Central zone, Tigray Region, Ethiopia.

Variables	Category	Cases	Controls	Total
		n=63(%)	n=252(%)	n=315(%)
Religion	Orthodox	54(85.7)	220(87.3)	274(87.0)
	Muslim and others	9(14.3)	32 (12.7)	41(13.0)
Residence	Urban	25(39.7)	155(61.5)	180(57.1)
	Rural	38(60.3)	97(38.5)	135(42.9)
Educational	Unable to write and read	20(31.7)	38(15.1)	58(18.4)
status	Primary school	17(27)	66(26.2)	83(26.3)
	Secondary school	18(28.6)	99(39.3)	117(37.1)
	Diploma and above	8(12.7)	49(19.4)	57(18.1)
Marital status	Married	51(81.0)	236(93.7)	287(91.1)
	Single	9(14.3)	14(5.6)	23(7.3)
	Divorced	3(4.8)	2(0.8)	5(1.6)
Occupational	Housewife	39(61.9)	118(46.8)	157(49.9)
status	Civil servant	6(9.5)	40(15.9)	46(14.6)
	Private worker	7(11.1)	46(18.3)	53(16.8)
	Farmer	5(7.9)	17(6.7)	22(7.6)
	Student	6(9.5)	31(12.3)	37(11.7)

Antepartum factors of study participants

Fifty-three (84.1%) cases and 227 (90.1%) controls had antenatal care follow up and 6 (9.5%) cases and 52.0% controls had pre-eclampsia. Fourteen (22.2%) cases and 62.4% controls were with the complication of polyhydramnios and 812.7% cases and 93.6% controls were had

oligohydramnios as a complication. Twelve 19.0 % cases and 93.6 % controls were anemic patients and 14 (22.2 %) cases and 14 5.6 % controls were had maternal infection. Six 1.9% cases had experience of having a history of smoking, 13 20.6 % cases and 4417.5 % controls had history abortion. Twenty-two 34.9 % cases and 101 (40.1 %) controls were primiparous parity.

Table 2: Distribution of antepartum factors of cases and controls attending public hospitals of Central zone, Tigray Region, North Ethiopia 2018.

Variables	Category	Cases	Controls	Total
		n=63(%)	n=252(%)	
ANC visit	Yes	53(84.1)	227(90.1)	280(88.9)
	No	10(15.9)	25(9.9)	35(11.1)
Preeclampsia	Yes	6(9.5)	5(2.0)	11(3.5)
	No	57(90.5)	247(98.0)	304(96.5)
Maternal DM	Yes	8(12.7)	8(3.2)	16(5.1)
	No	55(87.3)	244(96.8)	299(94.9)
Previous	Yes	8(9.1)	6(1.9)	14(4.4)
RH ⁺ Sensitization	No	55(90.9)	246(78.1)	301(95.5)
Antepartum	Yes	12(19.0)	8(3.2)	20(6.3)
hemorrhage	No	51(81.0)	244(96.8)	295(93.7)
Polyhydramnios	Yes	14(22.2)	6(2.4)	20(6.3)
	No	49(77.8)	246(97.6)	295(93.7)
Oligohydramnios	Yes	8(12.7)	9(3.6)	17(5.4)
0,	No	55(87.3)	243(96.4)	298(94.8)
Maternal	Yes	14(22.2)	14(5.6)	28(8.9)
infection	No	49(77.8)	238(94.4)	287(91.1)
Anemia	Yes	12(19.0)	6(2.4)	20(6.3)
	No	49(77.8)	246(97.6)	295(93.7)
History of	Yes	13(20.6)	44(17.5)	57(18.1)
abortion	No	50(79.4)	208(82.5)	258(81.9)
Alcohol	Yes	8(12.7)	5(2.0)	13(4.1)
	No	55(87.3)	247(98.0)	302(95.9)
Type of	Single	57(90.5)	239(94.8)	296(94.0)
pregnancy	Twin and above	6(9.5)	13(5.2)	19(6.0)
Maternal	Yes	14(22.2)	6(2.4)	20(6.3)
hypertension	No	49(77.8)	246(97.6)	295(93.7)
Medical problem	Yes	12(19.0)	26(10.3)	38(12.1)
	No	51(81.0)	226(89.7)	277(87.9)
Parity	Primiparous	22(34.9)	101(40.1)	123(39.0)
	Multiparous	41(65.1)	151(59.9)	192(61.0)
BMI	Underweight	11(17.5)	11(4.4)	22(7.0)
	Normal weight	39(61.9)	220(87.3)	259(82.2)
	Overweight	13(20.6)	21(8.3)	34(10.8)

Distributions of intrapartum and fetal factors among participants

Fifteen (23.8%) cases and 53(21.0%) controls were the experience of prolonged labor and 2 (3.2%) cases and 14 (5.6%) controls had a prolapsed cord as a complication of labor. Fifty-three (84.1%) cases and 185(73.4%)

controls delivered spontaneously and 34 (54.0%) cases and 224(88.9%) controls were born with the vertex presentation. Fifteen 23.8% cases and 23(9.1%) controls had meconium stained on pelvic examination. Thirty-six 5 (7.1%) cases and 43 (17.1%) controls were low birth weight and 4063.5% cases and 6827.0% and controls were preterm Table 3.

Variables	Category	Cases n=63(%)	Controls n=252(%)	Total
Prolonged labor	Yes	15(23.8)	53(21.0)	68(21.6)
	No	48(76.2)	199(79.0)	247(78.4)
Prolapsed cord	Yes	2(3.2)	14(5.6)	16(5.1)
	No	61(96.8)	238(94.4)	299(94.9)
Mode of delivery	Spontaneous	53(84.1)	185(73.4)	238(75.6)
	Instrumental	5(7.9)	21(8.3)	26(8.3)
	Cesarean	5(7.9)	46(18.3)	51(16.2)
	section			
Presentation	Vertex	34(54.0)	224(88.9)	258(81.9)
	Breech and	29(46.0)	28(11.1)	57(18.1)
	others			
Meconiumstained	Yes	15(23.8)	23(9.1)	38(12.1)
	No	48(76.2)	229(90.9)	277(87.9)
CPD	Yes	2(3.2)	10(4.0)	12(3.8)
	No	61(96.6)	242(96.0)	303(96.2)
PROM	Yes	14(22.2)	52(20.6)	66(21.0)
	No	49(77.4)	200(79.8)	249(79.0)
Placental	Yes	13(20.6)	8(3.2)	21(6.7)
abruption	No	50(79.4)	244(96.8)	294(93.3)
Weight of	<2.5kg	36(57.1)	43(17.1)	79(25.1)
newborn	≥2.5kg	27(42.5)	209(82.9)	236(74.9)
GA	<37weeks	40(63.5)	68(27.0)	108(34.8)
	≥37weeks	23(36.5)	184(73.0)	207(65.7)

Table 3: Distribution of intra-partum and fetal factors of cases and controls attending public hospitals of Central zone, Tigray Region, Ethiopia 2018.

Risk factors for stillbirth

In bivariate analysis, 17 variables showed a significant association with a stillbirth at a 25 % level of significance. Multivariable logistic regression was done by considering 17 variables simultaneously.

Maternal hypertension was showed a significant association with stillbirth. The odds of maternal hypertension were 12.83 times higher compared to those who were that [AOR=12.83; 95% CI 3.38, 48.83].

Polyhydramnios was significantly associated with stillbirth. Those who had polyhydramnios were 13.43 times more likely to deliver a still birth, as compared to those that didn't have it. [AOR=13.43; 95% CI 3.63, 49.67].

Drinking alcohol drinking was significantly associated with stillbirth. Mothers who drank alcohol were 7.56 times

more likely to deliver a still birth, as compared to those who didn't drink. [AOR=7.56; 95% CI 1.679, 34.04].

Status of meconium-stained liquor on pelvic examination had a significant association with the outcome variable of stillbirth. Those who had meconium stained liquor were 3.1 times more likely to deliver a still birth, as compared to those that did not have [AOR=7.88; 95% CI 1.73, 8.18].

Preterm babies were 2.6 times more likely to be still born, as compared to [AOR=2.6; 95%CI 1.119,6.158]. Similarly, the weight of the neonate also had a significant association with stillbirth. Low birth weight neonates had a 5.6 times higher risk of being still born, as compared to those with [AOR=5.6; 95% CI 2.393, 13.38] Table 4.

 Table 4: Bivariate and multivariable logistic regression among factors of cases and controls attending public hospitals of Central zone, Tigray Region, North Ethiopia 2018.

Variables	Category	Cases n=63(%)	Controls n=252(%)	COR [95%CI)	AOR [95%CL)
Residence	Urban	25(39.7)	155(61.5)	1	1
	Rural	38(60.3)	97(38.5)	2.429 (1.381,4.273)	1.209(0.558,2.024)
Educational status	Unable to write and	20(31.7)	38(15.1)	3.224(1.281, 8.113)	2.256(0.661,7.701)
	Primary school	17(27.0)	66(26.2)	1.575(0.630, 3.951)	1.707(0.553,5.269)
	Secondary school	18(28.6)	99(39.3)	0.982(0.435,2.217)	0.800(0.255,2.514)
	Diploma and above	8(12.7)	49(19.4)	1	1
ANC visit	Yes	53(84.1)	227(90.1)	1.713(0.776,3.782)	1.893(0.604,5.026)
	No	10(15.9)	25(9.9)	1	1
Maternal DM	Yes	8(12.7)	8(3.2)	4.436(1.598,12.336)	0.910(0.143,5.790)
	No	55(87.3)	244(96.8)	1	1
Maternal hypertension	Yes	14(22.2)	6(2.4)	11.71(4.291,31.98)	12.83(3.375,48.832) *
waternar nypertension	No	49(77.8)	246(97.6)	1	1
Maternal infection	Yes	14(22.2)	14(5.6)	4.85(2.178,10.532)	2.074(0.692,6.223)
	No	49(77.8)	238(94.4)	1	1
Antepartum	Yes	12(19.0)	8(3.2)	7.17(2.792,18.446)	2.218(0.673,7.311)
hemorrhage	No	51(81.0)	244(96.8)	1	1
Preeclampsia	Yes	6(9.5)	5(2.0)	5.2(1.533,17.636)	0.910(0.143,5.790)
ricecianipsia	No	57(90.5)	247(98.0)	1	1
Polyhydramnios	Yes	57(50.5)	247(50.0)	11.71(4291,31.980)	13.43(3.634,49.669)*
	No	14(22.2)	6(2.4)	1	1
	110	49(77.8)	246(97.6)	1	1
Alcohol	Yes	8(12.7)	5(2.0)	7.185(2.264,22.805)	7.561(1.679,34.044)*
	No	55(87.3)	247(98.0)	1	1
Oligohydramnios	Yes	8(12.7)	9(3.6)	3.927(1.480.10,636)	0.777(0.178,3.399)
	No	55(87.3)	243(96.4)	1	1
Weight of newborn	<2.5kg	36(57.1)	43(17.1)	6.481(3.566,11.776)	5.658(2.393,13.376) *
-	≥2.5kg	27(42.5)	209(82.9)	1	1
GA	<37weeks	40(63.5)	68(27.0)	4.706(2.626,8.434)	2.625(1.119,6.158) *
	≥37weeks	23(36.5)	184(73.0)	1	1
Meconiumstained	Yes	15(23.8)	23(9.1)	3.111(1.513,6.399)	3.15(1.73,8.179) *
	No	48(76.2)	229(90.9)	1	1
BMI	Underweight	11(17.5)	11(4.4)	0.177(0.072,0.437)	1.185(0252,5.603)
	Normal weight	39(61.9)	220(87.3)	0.619(0.209,1.832)	0.461(0.144,1.478)
	Overweight	13(20.6)	21(8.3)	1	1
Medical problem	Yes	12(19.0)	26(10.3)	2.045(0.968,4.323)	3.24(0.789,5.654)
	No	51(81.0)	226(89.7)	1	1
Placental abruption	Yes	13(20.6)	8(3.2)	7.936(3.123,20.135)	1.63(0.387,564)
1	No	50(79.4)	244(96.8)	1	1

Discussion

The study was aimed to assess risk factors of stillbirth. It attempted to look the determinants of stillbirth by incorporating as many risk factors as possible.

In this study, mothers with maternal hypertension had a significant risk of stillbirth. Those who had maternal hypertension were 12.83 times more likely to believe a still birth, when compared to those who were free of hypertension during pregnancy. This result is consistent with previous studies¹⁴⁻¹⁶. This may be due to the result of abruptio placentae, uteroplacental insufficiency, placental infarction, or fetal-maternal hemorrhage. Due to those reasons, maternal hypertension may decrease fetal growth. Fetal-maternal hemorrhage causes elevated maternal serum α -fetoprotein found to be a marker of stillbirth.

Birth weight showed a significant association with stillbirth. Low birth weight infants were 5.65 times more likely still born, when compared to normal weight \geq 2500g. This finding is similar to studies conducted in all over the world and Zimbabwe^{8,17} presented that low birth weight was a risk factor for stillbirth. This may be because low birth weight occurs due to a maternal complication like hypertension, diabetes mellitus that present pre-conception or antepartum.

Preterm birth had a 2.6 times higher risk of stillbirth than term birth. This study is in line with previous studies^{17,18}, which discovered that preterm babies were more at risk of being still born. This may be due to the fact that premature infants are more susceptible to ischemia, due to incomplete blood-brain barrier formation. Moreover, it may also be due to the fact that preterm babies face multiple morbidities, including organ system, dysfunction due to immaturity, especially lung immaturities causing respiratory failure.

Meconium stained liquor on pelvic examination of mothers had a significant association with stillbirth. Those who had meconium stained liquor were 13 times more likely to deliver a still birth, as compared to those who did not have meconium stained liquor. This result is in line with other previous studies^{19,20}. In healthy, well-oxygenated fetuses, this diluted meconium is readily cleared from the lungs by the normal physiological mechanism. However, in a few cases, meconium aspiration syndrome occurs, causing respiratory failure, and thus still births. Drinking alcohol had a significant association with the stillbirth. The odds of those who had drank of alcohol were 7.6 times higher than those who did not drink alcohol for the effect of stillbirth. This study is consistent with other studies^{21,22}. This may be due to the fact that mainly because of fetoplacental dysfunction. Another reason could be alcohol can result in low birth weight and preterm birth; those factors had an effect with a stillbirth.

Polyhydramnios had a significant association with stillbirth. Mothers who had polyhydramnios 13.43 times at higher risk than those who haven't had polyhydramnios to the outcome of stillbirth. This study is in line with studies reported previously^{23,24}. This could be due to the fact in the polyhydramnioscomplication there is premature labor because of the additional pressure stretching of the womb.Additionally, polyhydramnios can lead to the wrong position; the umbilical cord may slip down into the birth canal when the membranes rupture and an increased risk of bleeding after delivery. Consequently, the mother can have a stillbirth.

Conclusion

Stillbirth is one of the worldwide problems of newborns. There are different variables which affect stillbirth. Stillbirth risk increases with increase in maternal complication like hypertension, alcohol consumption, polyhydramnios, and meconium-stained amniotic fluid. The occurrence of preterm delivery, and low birth weight had an effect on the risk of stillbirth. Most of these variables are preventable by the holistic care of pregnancy, labor and delivery and post-natal care. Researchers should work on the prevention of stillbirths and give emphasis on the consequences of stillbirths.

Limitation

This study was quantitative, it would have been better if the qualitative approach was also employed to investigate in detail the extra determinants of stillbirth.

This study was conducted in one zone of the region, it would be better if another zone was incorporated into the study, for it would have a better generalization to the region.

Recall bias.

List of Abbreviations

ANC: Antenatal Care, AOR: Adjusted Odd Ratio, COR: Crudes Odd Ratio, PROM: Pre-Rupture of Membrane, **SPSS:** Statistics Package for Social Science, TRHB: Tigray Regional Health Bureau, WHO: World Health Organization,

Declaration

Ethics approval and consent to participate

Ethical clearance was obtained from Aksum University, college of health science, institutional review board AKU-CHS, IRB of the research committee. Respondents were informed about the purpose of the study; the information was collected after obtaining written consent from each participant. Written consent was obtained from all the informed respondents before the start of each interview. Respondents were allowed to refuse or discontinue their participation at any. Information was recorded anonymously and confidentiality and beneficence were assured throughout the study.

Availability of data and materials

There are no competing interests.

Competing interests

This manuscript maintains no competing financial interest declaration from any person or organization, or non-financial competing interests such as political, personal, religious, ideological, academic, intellectual, commercial or any other.

Funding

No funding source was received.

Acknowledgments

We would like to thank all study participants and data collectors for their contribution to the success of our work.

Authors' contributions

HT: Conceived and designed the study, analyzed the data and wrote the manuscript. MZ, GT, and TM were involved in data analysis, drafting of the manuscript and advising on the whole research paper, and were also involved in the interpretation of the data and contributed to manuscript preparation. Similarly, all authors read and approved the final version of the manuscript.

Consent to publish

Not applicable.

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