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Research Article

Risk Factors Associated with Intrauterine Fetal Death at the Kalaban-Coro Reference Health Center in Mali, 2023

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Abstract

Background: In-utero fetal death is a public health problem associated with several factors. The main objective was to study the factors associated with in-utero fetal death at the Kalaban-Coro referral health center in 2023. Methods: This was a case-control study including 70 cases and 134 controls. The study was conducted from July 1, 2023, to November 13, 2024. The cases were patients with fetal death who were not in labor, with a gestational age ≥ 22 weeks of amenorrhea or a fetal weight ≥ 500g and with a usable obstetric record. The controls were mothers who had given birth to live babies at term. The data were analyzed using SPSS version 21 software. Logistic regression was performed to identify the factors. The association was considered significant when the confidence interval excluded 1. The significance threshold was 5%. We adhered to the ethical principles of the Declaration of Helsinki. Results: The risk of intrauterine fetal death is five times higher in women with multiple pregnancies (aOR = 5.25; 95% IC: 1.05-26.29). This risk was 16 times higher in women who had experienced antepartum hemorrhage (aOR= 16.4; 95% IC: 1.33-202.7). The absence of prenatal care increased the risk of intrauterine fetal death by 45.37 times (aOR= 45.4; 95% IC: 2.38-866.4). Conclusion: Advanced prenatal care strategies are needed to reduce the burden of intrauterine fetal death.

Keywords

Intrauterine Fetal Death, Risk Factors, Kalaban-Coro, Mali

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1. Introduction

Intrauterine fetal death (IUFD) is defined as any fetal death occurring at 22 weeks of gestation or a birth weight of 500 g or less if gestational age is uncertain [1]. It constitutes a public health problem in low- and middle-income countries where healthcare provision is suboptimal. Worldwide, there are approximately 2 million intrauterine fetal deaths each year [2]. IUFD accounts for 2% of pregnancies worldwide [3]. In Serbia, the incidence of intrauterine fetal death was 0.08% in 2022 [4]. Three-quarters (¾) of intrauterine fetal deaths occur in sub-Saharan Africa or South Asia [2]. In the Democratic Republic of Congo, it accounts for 4% of deliveries at the Jason Sendwe Hospital in Lubumbashi [5]. The rate of stillbirth was 3.5% in Tanzania [6], 3.64% at the Sylvanus Olympio Teaching Hospital in Togo [7], and 3.69% in a level II maternity unit in Guinea [8]. In Mali, the rate of stillbirth was 1.43% of deliveries at the Commune IV referral health center [9].

Intrauterine fetal death is associated with several factors, as reported in the literature. Maternal factors include smoking, alcohol consumption, extreme maternal age, primiparity, placental abruption, infection during pregnancy, diabetes, and hypertensive disorders [3, 10]. Fetal factors include congenital malformations and growth restriction [11]. Despite progress in prenatal care, fetal death remains a problem due to its high frequency and the psychological burden it entails. In most cases, it remains unexplained [12]. Identifying risk factors is therefore a cornerstone of the fight against this tragic event. It would allow for better prevention through early detection and appropriate treatment.

The Kalaban-Coro referral health center is a primary peri-urban referral facility that performs more than 2,000 deliveries per year. However, data on risk factors for intrauterine fetal death are rarely used in this facility, hence the importance of this study to enable current professionals to understand the risk factors for intrauterine fetal death and contribute to improving the well-being of the mother-child dyad through the preventive management of intrauterine fetal death. The main objective was to study the factors associated with intrauterine fetal death at the Kalaban-Coro reference health center in 2023.

2. Materials and Methods

2.1. Study Setting

This study was conducted in the gynecology and obstetrics department of the Kalaban-Coro Reference Health Center (CSRef), a primary referral facility in Mali.

2.2. Study Type and Period

This was a case-control study with a ratio of 1 case to 2 controls, conducted from July 1st, 2023, to November 13th, 2024, a period of 13 months.

2.3. Study Population

The study included pregnant women who gave birth at the Kalaban-Coro Reference Health Center.

2.3.1. Inclusion Criteria

Cases were patients with fetal death who were not in labor, had a gestational age of 22 weeks or more of amenorrhea, or a fetal weight of 500g or more, and had a usable obstetric record.

Controls were two (2) mothers who delivered live at-term pregnancies immediately after the cases of fetal death. Thus, each case of intrauterine fetal death was compared to two controls. The matching variable was maternal age.

2.3.2. Non-inclusion Criteria

Fetal deaths occurring during delivery and those occurring before the threshold of fetal viability were not included in this study. Similarly, premature and post-term births in the control group were excluded to optimize the analysis.

2.3.3. Sampling Size and Technic

Cases and controls were recruited consecutively. For each case of intrauterine fetal death, two control deliveries were recruited, with age used as a matching variable. The sample size was calculated using statcalc on EpiInfo 7.2 (CDC, Atlanta, USA). The ratio was 1 case to 2 controls. The desired power was 80%, with a control proportion of 44.4%, based on the study conducted by Kangulu IB et al. [9] in the Democratic Republic of Congo in 2016. The minimum odds ratio was set at 2.5%, resulting in a sample size of 195 subjects, including 65 cases and 130 controls. In the study implementation, we included 70 cases and 134 controls.

2.4. Variables Studied

The variables of interest were sociodemographic: age (mean ± standard deviation), age group (20 to 34 years, ≤ 19 years, ≥ 35 years), schooling (yes, no), and occupation (housewife, other), marital status (married, single). The clinical and obstetric variables were: number of prenatal visits (none, 1 to 3, ≥ 4), gravidity (primigestive, small pregnancies, multigravestive, very multigravestive), parity (primiparous, small pregnancies, multiparous, very multiparous), gestational age in weeks (22 to 36 weeks, 37 to 41 weeks, ≥ 42 weeks), nature of pregnancy (single, multiple), mode of admission (self-admission, evacuated/referred), general condition (good, fair, poor), presence of fever (yes, no), fetal presentation (cephalic, dystocic), medical history (hypertension, diabetes, miscarriage, intrauterine fetal death, neonatal

death, cesarean section). The paraclinical variables were: blood glucose (normal, elevated, not measured), CRP (positive, negative, not measured), thick blood smear (positive, negative, not measured).

2.5. Data Collection and Analysis

Data were collected from obstetric records for all subjects included in the study. Data collection was performed using the Google Forms online tool. Data were analyzed using SPSS version 21. Descriptive statistics were calculated by determining frequencies and counts for categorical variables and the mean ± standard deviation for continuous variables. Binary logistic regression was performed to identify factors associated with intrauterine fetal death, with intrauterine fetal death as the dependent variable. Odds ratios (OR) were calculated with their confidence intervals (CI). An association was considered significant when the confidence interval excluded 1. The significance level was set at 5%.

2.6. Ethical Considerations

We adhered to the ethical principles outlined in the Declaration of Helsinki. All information gathered from the women involved remained confidential. Similarly, the participants' names were kept confidential and were not mentioned in the presentation of the results or associated with them in any way. Respect and confidentiality were upheld.

3. Results

3.1. Frequency of Intrauterine Fetal Death

During the study period, 5,064 deliveries were recorded, including 70 cases of intrauterine fetal death (IUFD), representing a hospital frequency of 1.38%.

3.2. Sociodemographic, Gynecological, and Obstetric Characteristics

In the study, the majority of patients were between 20 and 34 years old (71.4% of cases) and 75.4% of controls. 56% of participants had attended school, compared to 67% of controls. Housewives represented 77% of cases and 65% of controls. Married women represented 85.7% of cases and 94.8% of controls (Table 1). In the control group, 22.9% of participants had attended at least four prenatal consultations, compared to 70.1% of controls. Women with multiple pregnancies and those with few pregnancies were the most represented, at 30% each in the case group, and 24.6% and 23.9% respectively in the control group. The gestational age was between 28 and 36 weeks in 52.9% of the case group compared to 1.5% in the control group. For both the case and control groups, the pregnancy was singleton in 97.1% and 97% respectively (Table 1).

Table 1. *Sociodemographic Characteristics of Women Who Gave Birth at the Kalaban-Coro Referral Health Center in 2024 included in the Study.*

	Case		**Control**	
	n =70	**%**	**n=134**	**%**
Age category				
20 to 34	50	71.4	101	75.4
≤ 19	10	14.3	14	10.5
≥ 35	10	14.3	19	14.2
Schooling				
Schooled	39	56.0	90	67.0
Not in school	31	44.0	44	33.0
Occupation				
Homemaker	54	77.0	87	65.0
Other	16	23.0	47	35.0
Marital status				
Married	60	85.7	127	94.8
Single	10	14.3	7	5.2
Number of prenatal visits				

	Case		Control	
	n =70	%	n=134	%
0	11	15.7	1	0.7
1 to 3	43	61.4	39	29.1
≥ 4	16	22.9	94	70.1
Gestation				
First pregnancy	11	15.7	35	26.1
Short pregnancy	20	28.6	52	38.8
Multiple pregnancy	21	30.0	33	24.6
Highly multiparous	18	25.7	14	10.4
Parity				
Nulliparous	3	4.3	0	0.0
First pregnancy	8	11.4	37	27.6
Short pregnancy	20	28.6	51	38.1
Multiparous	21	30.0	32	23.9
Highly multiparous	18	25.7	14	10.4
Gestational age in weeks				
28 to 36 weeks	37	52.9	2	1.5
37 to 41 weeks	32	45.7	132	98.5
≥ 42 weeks	1	1.4	0	0.0
Type of pregnancy				
Single	68	97.1	130	97.0
Multiple	2	2.9	4	3.0

Other* Student; Teacher/Secretary; Salesperson/Shopkeeper; Seamstress

3.3. Clinical and Paraclinical Characteristics

Patients were in good general condition in 81.4% of cases and 98.5% of controls. Fetal presentation was cephalic in 88.6% of cases and 96.3% of controls. A history of hypertension was found in 21.4% of cases versus 9% of controls. Diabetes was present in 8.6% of cases and 5.2% of controls. A history of miscarriage was found in 15.7% of cases versus 20.9% of controls. We recorded a history of intrauterine fetal death (IUFD) in 17.1% of cases versus 13.4% of controls. A history of neonatal death and cesarean section represented 8.6% each in cases and 14.9% and 2.2%, respectively, in controls (Table 2). Blood glucose levels were normal in 65.7% of the case group and 82.8% of the control group. C-reactive protein (CRP) and thick blood smear were positive in 10% and 44.3% of the case group, respectively, and in 8.2% and 16.4% of the control group.

Table 2. *Clinical Characteristics of Women Who Gave Birth at the Kalaban-Coro Referral Health Center in 2024 Included in the Study.*

	Case		Control	
	n =70	%	n=134	%
General condition				

	Case		Control	
	n =70	%	n=134	%
Good	57	81.4	132	98.5
Fair	12	17.1	2	1.5
Impaired	1	1.4	0	0.0
Fetal presentation				
Cephalic	62	88.6	129	96.3
Non-cephalic	8	11.4	5	3.7
History of hypertension				
Yes	15	21.4	12	9.0
No	55	78.6	122	91.0
History of diabetes				
Yes	6	8.6	7	5.2
No	64	91.4	127	94.8
History of abortion				
Yes	11	15.7	28	20.9
No	59	84.3	106	79.1
History of IUFD				
Yes	12	17.1	18	13.4
No	58	82.9	116	86.6
History of neonatal death				
Yes	6	8.6	20	14.9
No	64	91.4	114	85.1
History of cesarean section				
Yes	6	8.6	3	2.2
No	64	91.4	131	97.8

3.4. Risk Factors for Intrauterine Fetal Death

In univariate analysis, the factors associated with intrauterine fetal death were chronic hypertension (crude OR=14.78; 95% CI [1.78-122.70], p=0.013), pre-eclampsia/eclampsia (crude OR=6.19; 95% CI [1.22-31.51], p=0.028), high multigender pregnancies (crude OR=3.97; 95% CI [1.50-10.53], p=0.006), multiparity (crude OR=3.27; 95% CI [1.29-8.29], p=0.012) and high multiparity (crude OR=5.79; 95% CI [2.05-16.32], p=0.001), History of neonatal death (crude OR=3.40; 95% CI [1.62-7.14], p=0.001), antepartum hemorrhage (crude OR=11; 95% CI [2.34-51.75], p=0.002), absence of prenatal care (crude OR=42.78; 95% CI [4.86-376.25], p=0.001), severe iron deficiency anemia (crude OR=5.82; 95% CI [2.14-15.79], p=0.001), and malaria (crude OR=2.87; 95% CI [1.15-7.20], p=0.024) (Table 3).

In the final logistic regression model, the risk of intrauterine fetal death (IUFD) was five times higher in women with multiple pregnancies (aOR = 5.25; 95% CI [1.05–26.29], p = 0.044). This risk was 16 times higher in women who had experienced antepartum hemorrhage (aOR = 16.42; 95% CI [1.33–202.76], p = 0.029). The absence of prenatal care increased the risk of intrauterine fetal death by 45.37 times (aOR = 45.37; 95% CI [2.38–866.39], p = 0.001) (Table 3).

Table 3. *Factors Associated with Intrauterine Fetal Death at the Kalaban Coro Referral Health Center in 2023.*

	OR [95% CI]	p	aOR [95%CI]	p
Category of age				
20-34	____	__	____	__
≤ 19	1.40 [0.59-3.48]	*0.41*	1.70 [0.34-8.76]	*0.52*
≥ 35	1.10 [0.46-2.46]	*0.89*	0.41 [0.11-1.47]	*0.17*
Schooling				
Schooled	____	__	____	__
Not in school	1.60 [0.89-2.94]	*0.11*	0.92 [0.38-2.21]	*0.85*
Occupation				
Housewife	____	__	____	-
Other	0.50 [0.28-1.06]	*0.08*	0.77 [0.30-1.99]	*0.59*
Chronic Hypertension				
No	____	__	____	__
Yes	14.80 [1.78-122.76]	*0.01*	12.7 [0.48-336.20]	*0.13*
Diabetes during pregnancy				
No	____	__	____	__
Yes	1.93 [0.12-31.29]	*0.64*	2.05 [0.04-95.40]	*0.71*
Preeclampsia/Eclampsia				
No	____	__	____	__
Yes	6.19 [1.22-31.51]	*0.03*	1.35 [.038-47.80]	*0.87*
Gestation				
First pregnancy	____	__	____	__
Short pregnancy	1.21 [0.52-2.85]	*0.66*	2.61 [0.69-9.93]	*0.16*
Multiple pregnancy	1.91 [0.80-4.56]	*0.15*	-	-
Highly multiparous	3.97 [1.50-10.53]	*<0.01*	5.25 [1.05-26.29]	*0.04*
Parity				
First pregnancy	____	__	____	__
Short pregnancy	1.77 [0.70-4.45]	*0.22*	-	-
Multiple pregnancy	3.27 [1.29-8.29]	*0.01*	-	-
Highly multiparous	5.79 [2.05-16.32]	*<0.01*	-	-
History of stillbirth				
No	____	__	____	__
Yes	1.33 [0.60-2.95]	*0.48*	2.44 [0.66-9.02]	*0.18*
Intrauterine growth restriction				
No	____	__	____	__
Yes	0.16 [0.02-1.28]	*0.09*	0.16 [0.02-1.28]	*0.09*
History of neonatal death				
No	____	__	____	__

	OR [95% CI]	p	aOR [95%CI]	p
Yes	3.40 [1.62-7.14]	*<0.01*	2.30 [0.86-6.18]	*0.10*
Ante-patopartum hemorrhage				
No	———	—	———	—
Yes	11 [2.34-51.75]	*<0.01*	16.4 [1.33-202.7]	*0.03*
Number of prenatal visits				
0	42.8 [4.9-376.2]	*<0.01*	45.4 [2.38-866.4]	*0.01*
1-3	2.72 [1-7.41]	*0.05*	3.14 [0.84-11.75]	*0.09*
≥ 4	———	—	———	—
Fetal presentation				
Cephalic	———	—	———	—
No cephalic	1.93 [0.12-31.29]	*0.04*	0.14 [0.03-0.80]	*0.03*
Retro-placental hemorrhage				
No	———	—	———	—
Oui	8.06 [0.88-73.56]	*0.06*	1.53 [0.06-39.37]	*0.78*
Maternal anemia				
No	———	—	———	—
Yes	5.82 [2.14-15.79]	*<0.01*	3.032 [0.66-13.94]	*0.15*
Malaria				
No	———	—	———	—
Yes	2.87 [1.15-7.20]	*0.02*	1.72 [0.56-5.30]	*0.35*
Upper urinary tract infection				
No	———	—	———	—
Yes	0.48 [0.15-1.51]	*0.20*	0.218 [0.031-1.536]	*0.13*
Fetal-maternal incompatibility				
No	———	—	———	—
Yes	0.48 [0.20-1.18]	0.11	0.56 [0.17-1.85]	0.34

4. Discussion

4.1. Frequency of Intrauterine Fetal Death

The hospital prevalence of intrauterine fetal death was 1.38% in deliveries at the Kalaban-Coro Referral Health Center. Our prevalence differs from that reported by Kangulu et al., which was 13.98% [13] in 2015 and 5.6% [14] in the third trimester in 2022 in the Democratic Republic of Congo. In Guinea, Diallo et al. [15] reported a prevalence of 6.95% of deliveries at the Mamou Regional Hospital in 2016. In contrast, in France, the prevalence of Intrauterine fetal death is between 0.32% and 0.44% of deliveries [16]. The high prevalence of intrauterine fetal death in our context could be explained by the low utilization of healthcare services by the population due to low purchasing power. On the other hand, regarding the behavior of pregnant women in semi-rural areas with respect to prenatal consultations, most women seek prenatal care services late or only when problems exceed their ability to manage them through self-medication.

4.2. Patient Characteristice

The majority of patients were young, married housewives. The same observation was made by Traore FB et al. [17], who reported in their study that their patients were predominantly housewives and married. Diallo MH et al. [15] reported a young study population, with 72.7% of cases and 77.3% of

controls aged 20 to 34 years, and 81.8% of cases and 95.5% of controls aged 34 to 34 years. These results could be explained by the fact that this period corresponds to the time of sexual activity, but also the period when women are more willing to have children. Nevertheless, we found women under 20 years of age and women over 34 years of age. These age groups constitute risk factors for several complications during pregnancy, according to the literature [3, 6]. The participants were educated (56% of cases and 67% of controls). However, Kanagulu et al. [14] in 2023 reported that 52.6% of patients in their study in the Democratic Republic of Congo were uneducated. Schooling could promote access to healthcare, especially prenatal consultations, and also the adoption of preventive measures against pregnancy complications.

4.3. Factors Associated with Stillbirth

In univariate logistic regression analysis, chronic hypertension increased the risk of intrauterine fetal death by 14.78 times (p=0.013). Our result is comparable to those in the literature; Dangal et al. [18] in Nepal in 2023 found that pregnancy-induced hypertension was a factor in stillbirth. Preeclampsia/eclampsia was associated with a 6.19-fold increased risk of intrauterine fetal death (p=0.028). According to the literature, hypertensive disorders are significant risk factors for intrauterine fetal death. This risk is 2.48 [1.36–4.51] for all types of hypertensive disorders, 2.04 [1.47–2.81] for chronic hypertension, 4.30 [0.31–59.05] for gestational hypertension, and 2.32 [1.52–3.5] for preeclampsia [16, 19, 20]. These hypertensive disorders could lead to disruption of placental function with direct consequences on fetal perfusion, resulting in fetal death. Severe iron deficiency anemia (OR crude = 5.82; 95% CI [2.14–15.79]) and malaria (OR crude = 2.87) are also significant risk factors. The 95% CI [1.15-7.20] were risk factors in our univariate analysis. In the study by Chuwa et al. [6], preeclampsia was associated with a 4-fold increased risk of intrauterine fetal death (IUFD) (95% CI [3.38-4.97]), and anemia increased the risk of IUFD by 1.69-fold (95% CI [1.17-2.44]). Since the mother is the primary source of nutrition and development for the fetus, micronutrient deficiency exposes the fetus to the risk of growth restriction and IUFD. In cases of non-cephalic fetal presentation, the risk of IUFD was 1.93 times higher, and there was a significant association between IUFD and non-cephalic fetal presentations. The literature indicates that breech presentation, abnormal fetal position, and dystocia operate through similar mechanisms. the fetus is trapped in the birth canal and is subjected to hypoxia leading to an IUFD [21].

After adjusting for confounding factors, the following factors remained significantly associated with intrauterine fetal death in the final logistic regression model: high multiparity, antepartum hemorrhage, and lack of prenatal care. The risk of intrauterine fetal death is five times higher in high multiparity women. In the study by Kangulu et al. [13], multiparity increased the risk of intrauterine fetal death by 3.2 times, as did multiparity, which increased it by 2.9 times. These data are consistent with the literature, which indicates that multiparous and multigravida women are also more often of advanced maternal age and are at risk of certain conditions implicated in the causes of intrauterine fetal death, such as placenta previa, placental abruption, hypertension, diabetes mellitus, obesity, and intrauterine growth restriction [22]. Indeed, these conditions, associated with multiple pregnancies and multiple parities, amplify the risk of stillbirth. Conditions such as diabetes and hypertension have a complex course, especially during pregnancy. They disrupt the exchange of nutrients and oxygen between mother and fetus, exposing the fetus to a high risk of intrauterine death.

The risk was 16 times higher in women who had experienced antepartum hemorrhage (95% CI [1.33-202.76]). In their study, Dangal et al. [18] reported antepartum hemorrhage as a risk factor for stillbirth. Antepartum hemorrhages are relatively common during pregnancy and are caused by placenta previa and placental abruption. These abnormalities threaten the lives of both the mother and the fetus. They disrupt the exchange of nutrients and oxygen between mother and fetus. Its management is multidisciplinary (gynecologists-obstetricians, anesthesiologists-intensivists, midwives, biologists, and interventional radiologists), based on therapeutic protocols, and time is of the essence for the prognosis. Early detection is necessary to limit complications.

The absence of prenatal care increased the risk of intrauterine fetal death by 45.37 times (95% CI [2.38-866.39]). This result is comparable to that of Vintzileos et al. [23], who showed a tripled risk if the woman had never attended prenatal care. Similarly, Chuwa et al. [6] in Tanzania reported that the risk of intrauterine fetal death is doubled when there are fewer than four prenatal care visits (95% CI [1.83-2.45]). Prenatal care allows for the early detection and management of high-risk pregnancies. In the context of limited resources, prenatal care may be perceived as an expense by the population, explaining its non-observance. Awareness campaigns are of paramount importance to explain to the population the benefits of prenatal care, the importance of early management of pathologies during pregnancy, and especially the consequences of not attending prenatal care.

4.4. Strengths and Limitations of the Study

This was the first study to use regression analyses to eliminate confounding factors associated with intrauterine fetal death (IUFD) in our facility. The study was conducted in a primary referral center that receives patients from diverse socio-cultural and economic backgrounds, thus ensuring good sample representativeness. However, data were collected using obstetric records, which could introduce information bias. The selection of controls could be affected by the matching method.

5. Conclusion

The frequency of intrauterine fetal death remains unacceptably high in our healthcare facility and it driven by multiple, largely preventable factors, notably high rates of multi-pregnancies, antepartum hemorrhage, and inadequate utilization of prenatal care services. These findings underscore an urgent need to strengthen prenatal care policies, with particular emphasis on early identification and close monitoring of high-risk pregnancies. Health policy should prioritize the systematic screening and timely management of obstetric hemorrhage through standardized clinical protocol, continuous training of healthcare providers, and improved availability of essential diagnostic and therapeutic resources at the peripheral and referral facilities. Alongside, targeted community-based awareness campaigns should be intensified to improve knowledge of the benefits of early regular prenatal care. Also, policies to improve geographical accessibility through advanced prenatal consultations and financial accessibility through subsidies for additional assessments could reduce the burden of intrauterine fetal death.

Abbreviations

IUFD	Intrauterine Fetal Death
OR	Odds Ratio
aOR	Adjusted Odds Ratio

Author Contributions

Abou Sogodogo: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft

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Salia Keita: Conceptualization, Methodology, Supervision, Validation, Visualization, Writing – original draft

Mahamoudou Coulibaly: Data curation, Methodology, Resources, Conceptualization, Methodology, Writing – review & editing

Oumar Sangho: Methodology, Writing – review & editing

Cheick Abou Coulibaly: Methodology, Resources, Supervision, Writing – review & editing

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Borodjan Diarra: Conceptualization, Methodology, Supervision, Validation, Visualization, Writing – review & editing

Abdoul Salam Diarra: Conceptualization, Methodology, Supervision, Validation, Visualization, Writing – review & editing

Hamadoun Sangho: Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing

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Data Availability Statement

All materials and data used in this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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