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Effect of Maternal Beta-Thalassemia Minor on Obstetrical and Neonatal Outcomes in Kirkuk Province, Iraq

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ABSTRACT

Background: Maternal beta-thalassemia minor may increase the risk of adverse obstetrical outcomes like higher risk of fetal growth restriction, low birth weight, and preterm delivery.
Objectives: To determine maternal and neonatal outcomes in pregnant women with beta-thalassemia minor in Kirkuk province, Iraq.
Materials and methods: A case-control study was conducted and enrolled 95 pregnant women with beta-thalassemia minor and 100 control pregnant women without beta-thalassemia minor. A comparison between the two groups was performed regarding the general characteristics of the pregnant women, obstetrical complications, and neonatal outcomes.
Results: The mean hemoglobin (Hb), gestational age, and birth weight were significantly lower in the cases compared to the control group, with a P-value < 0.001, 0.002, and 0.004, respectively. Blood transfusion, emergency caesarean section (CS), postpartum hemorrhage, preterm labor, small for gestational age (SGA), and admission to the neonatal care unit (NCU) in cases were significantly higher compared to the control group. Admission to NCU was higher with low maternal Hb, lower gestational age at the time of delivery, pregnancies complicated by diabetes mellitus, oligohydramnios, meconium-stained liquor, preterm labor, pregnant women who delivered by CS, neonates with SGA , and those with a low APGAR (A= appearance, P = pulse rate, G = grimace, A = activity, and R = respiration) score.
Conclusion: Beta-thalassemia minor may adversely affect pregnancy outcomes and increase the frequency of neonatal admission to NCU.
Keywords: Beta-thalassemia minor; Maternal outcomes; Neonatal outcomes.

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INTRODUCTION

The most common causes of hypochromic microcytic anemia are iron deficiency anemia followed by the beta thalassemia trait [1]. Beta-thalassemia is a heterogeneous genetic abnormality due to mutations in genes responsible for beta chain production that cause decreased or absent beta chains leading to decreased hemoglobin, decreased erythropoiesis, and anemia [2]. The carriers of beta thalassemia minor are usually asymptomatic. Their hematological parameters are mostly mild hypochromic microcytic anemia, a high HbA2 level, with a normal or mildly elevated HbF level on Hb electrophoresis [3, 4]. In addition, there will be a reduced mean cell volume and a reduced mean corpuscular Hb. Pregnant women with thalassemia minor have more significant anemia. It is more common in the latter half of the second trimester and at the beginning of the third trimester [5, 6].

There is no specific treatment for thalassemia minor in pregnancy apart from folic acid. A blood transfusion is indicated in the presence of severe anemia during pregnancy. Physiological changes in the hematology system during pregnancy will worsen the severity of anemia. In several studies, it has been shown that there is an association between maternal thalassemia minor and adverse obstetric outcomes such as a higher risk of fetal growth restriction, low birth weight, and preterm birth [7, 8].

Regarding the prevalence of thalassemia minor in Iraq, sev-

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eral studies evaluated the prevalence in several regions; for example, in Baghdad, the prevalence was 4.4% as reported by Yahya in 1996 [9], while in Mosul city in the north of Iraq, the estimated prevalence was 8.8% as noticed in 2009 by Khaleel et al. [10]. In Basra, in the South of Iraq, 4.6% was the prevalence, as studied by Hassan in 2003 [11]. In Sulaymaniyah, it was 4.14% as seen by Jalal in 2008 [12]. Addressing thalassemia syndromes during pregnancy presents several challenging aspects, given their potential to impact both maternal and neonatal conditions. Therefore, special attention must be devoted to these women to comprehensively address the complexities involved. Additionally, there was no previous investigation in our city. Hence, we conducted this study to compare maternal and neonatal outcomes in pregnant women with or without beta-thalassemia minor in Kirkuk province, Iraq. The second goal was to recognize maternal complications that affect neonatal admission to the neonatal care unit (NCU) in pregnant women with beta-thalassemia minor.

MATERIALS AND METHODS

The current analysis was a case-control study carried out in the Department of Obstetrics of Azadi Teaching Hospital in Kirkuk City, Iraq, during the period from 1 May 2022 to 1 May 2023. The inclusion criteria of the case group were pregnant women admitted to the hospital for labor or elective caesarean section (CS) and diagnosed with beta-thalassemia minor by the hematologist during or before pregnancy. The control group was pregnant women admitted to the hospital for labor or elective CS with normal hemoglobin electrophoresis.

Exclusion criteria were gestational age < 24 weeks and > 42 weeks, multiple pregnancies, congenital fetal anomalies, fetal chromosomal abnormalities e.g., Down's syndrome, maternal smoking, Rh-ve women, chronic hypertension, pre-pregnancy diabetes mellitus, other hemoglobinopathy, maternal age over 40 years, and those who didn't want to participate in the study.

The study was conducted per the ethical principles that have their origin in the Declaration of Helsinki. We obtained the written consent from all participants. The study protocol, the subject information, and the consent form were reviewed and approved by a local ethics committee according to document number 20 on 18/12/2022 to get this approval.

A sample of 95 pregnant women with beta-thalassemia minor (87 of them were previously diagnosed and 8 of them were diagnosed at the time of admission to the hospital) and 100 control pregnant women without beta-thalassemia minor were enrolled in the present study. Information and parameters about pregnant women collected either directly by the researcher or from patient records include:

1. General characteristics of pregnant women (maternal age, parity, and mode of delivery).
2. Obstetrical complications (preeclampsia, maternal diabetes, antepartum hemorrhage, polyhydramnios, oligohydramnios, meconium-stained liquor, blood transfusion during pregnancy or in the postpartum period, and postpartum hemorrhage).
3. Neonatal outcomes of pregnant women (gestational age at the time of delivery, birth weight, intrauterine death, intrapartum death, APGAR (A= appearance, P = pulse rate, G = grimace, A = activity, and R = respiration) score less than 7 at 5 minutes, and admission to the neonatal care unit).

The mode of delivery (vaginal delivery, elective CS, emergency CS, or instrumental vaginal delivery) was decided by the responsible obstetrician in the labor ward according to the status of pregnant women and their preferences. The APGAR score and other neonatal outcomes were evaluated by the pediatrician. The APGAR score was classified into normal (7), intermediate (4–6), and low (< 4). Birth weight was plotted on the growth chart; less than the 10^{th} centile was regarded as small for gestational age.

The blood sample (4 ml) was taken and sent to the lab for a complete blood count, blood group and Rh, random blood sugar, and serum ferritin for all pregnant women who enrolled in the study. To choose the control group, another blood sample (2 ml) was taken and sent to the hematologist for Hb electrophoresis. Anemia is defined as a hemoglobin level below 10.5 g/dl in the second and third trimesters.

Statistical analysis was done using SPSS version 26. Continuous data were presented as a mean value with a standard deviation (SD), and categorical variables were summarized as numbers (no) and percentages (%). Comparisons between groups were made using Chi-square tests for categorical variables, independent sample t-tests for normally distributed continuous variables, and Mann-Whitney tests for non-normally distributed continuous variables. A grouped scatter graph was used to clarify the correlation between some variables. A P-value of < 0.05 is considered a statistically significant difference.

RESULTS

According to the haematologist's decision, 100 pregnant women with normal Hb electrophoresis were in the control group, and 95 pregnant women with beta-thalassemia minor were in the case group . The mean values of the Hb level (9.8 ± 1.4 g/dl), gestational age (37.5 ± 3.2 weeks), and birth weight (2.9 ± 0.9 Kg) in the case group, were significantly lower than in the control group with a P-value of 0.001, 0.002, and 0.004, respectively. Although the mean age value in the case group (27.5 ± 6.9 weeks) was lower than in the control group (27.7 ± 6.8 weeks), this relationship was not statistically significant. The mean value of parity is the same in both groups, as shown in Table 1.

Regarding obstetric risk factors such as preeclampsia (PET), gestational diabetes mellitus (GDM), antepartum hemorrhage (APH), polyhydramnios and/or oligohydramnios, and meconium-stained liquor (MSL), there were no statistically significant differences between both groups (P-value $>$ 0.05). During pregnancy, 56.8% of cases needed blood transfusions compared to the control group (only 10% of them

Table 1. Demographic and clinical characteristics of the studied groups*.

Variables	Case group Mean ± SD	Control group Mean ± SD	P-value
Maternal age (year)	27.5 ± 6.9	27.7 ± 6.8	0.827
Parity	2.3 ± 2.2	2.3 ± 2.2	0.938
Maternal Hb (g/dl)	9.8 ± 1.4	10.8 ± 1.2	0.001•
Gestational age (week) †	37.5 ± 3.2	38.6 ± 2.7	0.002•
Birth weight (Kg)	2.9 ± 0.9	3.3 ± 0.7	0.004•

* Independent sample t test, •Significant (P-value < 0.05)
† Mann-Whitney tests

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needed blood), which was statistically significant with a P-value of 0.001 as shown in Table 2.

In terms of delivery mode, 53.7% of the case group were delivered by emergency CS, while in the control group, 54% were delivered vaginally (P-value = 0.001). Postpartum hemorrhage (PPH) occurred in 17.9% of the case group, and 24.2% of them needed blood; unlike the control group, only 2% of them developed PPH, and 7% of them needed blood after delivery; these relations were statistically significant differences with a P-value of 0.001.

Regarding neonatal outcome, 23.2% of newborns in the case group were SGA, and 66.3% of them were admitted to the NCU, unlike newborns in the control group, of whom only 7% were SGA and only 13% needed admission to the NCU. Also, this relationship had a statistically significant difference with a P-value of 0.002 and 0.001, respectively. In the case group, 14.7% of newborns with an APGAR score less than 7 at 5 minutes and eight babies died [6 intrauterine fetal deaths (IUFD) and 2 intrapartum deaths], while in the control group, 10% had a low APGAR score, 4 IUFD, and 1 intrapartum death, as shown in Table 3.

In the case group, most of the newborns who needed admission to the NCU were babies of mothers with a low mean value of Hb, gestational age, who had GDM (100%), oligohydramnios (100%), MSL (90.9%), who were delivered by CS (75.4%) with a low mean value of birth weight, and APGAR score < 7 at 5 minutes (100%) compared to newborns not admitted to the NCU. These associations were statistically significant differences, as shown in Table 4.

There was a significant correlation between the birth weight of the newborns and the maternal Hb level, as shown in Figure 1.

DISCUSSION

During pregnancy, individuals with beta-thalassemia minor may experience mild anemia during pregnancy due to ineffective erythropoiesis rather than hemolysis [13]. In some cases, anemia can worsen due to subnormal erythropoiesis accompanying normal plasma volume expansion, leading to increased severity [14]. The differentiation between ineffective erythropoiesis and hemolysis is crucial in understanding the specific challenges and potential interventions required to manage anemia effectively in this population. A key strength of our research lies in the substantial sample size, which allowed us to collect robust data for our analysis. Furthermore, our study focused on a specific population of pregnant women in Kirkuk City, Iraq, which contributes to the existing literature by examining thalassemia minors in an understudied context.

In our study, we found a significantly lower mean Hb level in patients than in the case group, aligning with the findings of Ruangvutilert et al., (2023) [15]. This convergence reinforces the notion that the thalassemia trait increases the risk of maternal anemia during pregnancy. It is essential to recognize that maternal anemia can potentially lead to adverse consequences for both the mother and the developing fetus. Our research highlights the clinical significance of addressing and managing anemia in pregnant individuals with thalassemia minor to optimize maternal and neonatal health.

Interestingly, while the mean maternal age in the case group was lower than in the control group, the difference was

Table 2. Obstetric complications in patients and control groups*.

Variables	Case group(95) N(%)	Control group(100) N(%)	P-value
Preeclampsia	16(16.8%)	9(9%)	0.102
Gestational diabetes mellitus	11(11.6%)	12(12%)	0.927
Antepartum hemorrhage	8(8.4%)	6(6%)	0.513
Polyhydramnios	3(3.2%)	7(7%)	0.224
Oligohydramnios	12(12.6%)	8(8%)	0.287
Meconium-stained liquor	11(11.6%)	11(11%)	0.898
Antepartum Blood transfusion	54(56.8%)	10(10%)	0.001†

* Chi-square test, †Significant (P-value < 0.05)

Table 3. Labor complications and neonatal outcomes of case and control groups*.

Complications	Case group(95) N(%)	Control group(100) N(%)	P-value
Mode of delivery			
Vaginal delivery	28(29.5%)	54(54%)	0.001†
Instrumental vaginal delivery	2(2.1%)	7(7%)	0.103
Elective CS	14(14.7%)	14(14%)	0.883
Emergency CS	51(53.7%)	25(25%)	0.001†
Postpartum hemorrhage	17(17.9%)	2(2%)	0.001†
Postpartum Blood transfusion	23(24.2%)	7(7%)	0.001†
Preterm labor	16(16.8%)	7(7%)	0.033†
Intrauterine fetal death	6(6.3%)	4(4%)	0.464
Intrapartum death	2(2.1%)	1(1%)	0.531
APGAR score < 7	14(14.7%)	10(10%)	0.314
Small for gestational age	22(23.2%)	7(7%)	0.002†
Neonatal care unit admission	63(66.3%)	13(13%)	0.001†

* Chi-square test, †Significant (P-value < 0.05), CS = Caesarean section

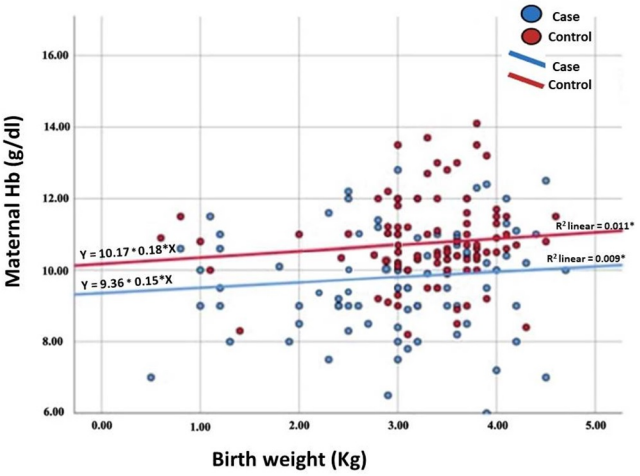

Figure 1. A grouped scatter of maternal Hb level during pregnancy by birth weight in the two groups. Y= mean Hb in the case and control groups, X = Birth weight, and R2 = coefficient of determination.

Table 4. Association of maternal complications with neonatal admission to NCU in the thalassemic mother*.

Variables	NCU admission (63) N(%)	Non-admitted NCU (32) N(%)	P-value
Maternal age (year)	27.7 ± 7.1	27.3 ± 6.6	0.629
Maternal Hb (g/dl)	9.6 ± 1.5	10.1 ± 1.1	0.017†
Gestational age (week)	36.9 ± 3.7	38.5 ± 7.1	0.002†
Birth weight (Kg)	2.836 ± 1.039	3.156 ± 0.558	0.007†
Preeclampsia	12 (75%)	4 (25%)	0.420
Gestational diabetes mellitus	11 (100%)	0 (0%)	0.012†
Antepartum hemorrhage	7 (87.5%)	1 (12.5%)	0.185
Polyhydramnios	3(100%)	0 (0%)	0.210
Oligohydramnios	12 (100%)	0 (0%)	0.008†
Meconium-stained liquor 10	(90.9%)	1 (9.1%)	0.031†
Vaginal delivery	14 (46.7%)	16 (53.3%)	0.006†
Caesarean section	49 (75.4%)	16(24.6%)	0.006†
Preterm labor	15 (93.7%)	1 (6.3%)	0.011†
Small for gestational age	18 (81.8%)	4 (18.2%)	0.079
APGAR score < 7	14 (100%)	0 (0%)	0.004†

* Independent sample t test, †Significant (P-value < 0.05), Chi-square test

not statistically significant. However, the gestational age in the case group was significantly lower in comparison to the control group, which aligns with the findings of Leuwan et al., (2009) [7]. These findings may suggest that, despite being younger, pregnant individuals with thalassemia minor experience a shortened gestational period, potentially due to various physiological factors related to the condition. Understanding the impact of thalassemia minor on gestational age can help healthcare providers tailor care plans and anticipate potential complications associated with preterm births.

Our research also revealed a significantly lower birth weight in newborns of mothers with thalassemia minor, consistent with the findings of Charoenboon et al., (2016) [13]. This emphasizes the importance of closely monitoring fetal growth and development in pregnancies affected by thalassemia minor and implementing appropriate interventions to optimize birth outcomes. Low birth weight is a well-known risk factor for neonatal morbidity and mortality and can have long-term implications for the health and development of the child.

Comparing our study to the research conducted by Adler et al., (2021) [16], we identified both similarities and differences in our findings. The shared findings of significantly lower mean Hb levels and a lower gestational age in the case group indicate a consistent association between thalassemia minor and adverse perinatal outcomes. This consistency strengthens the evidence supporting the link between thalassemia minor and maternal anemia and potential complications related to fetal growth and development. However, variations in the focus on specific outcomes, such as gestational diabetes and preeclampsia, highlight the complexity of the relationship between thalassemia minor and obstetric complications. These variations underscore the importance of considering factors such as study design, sample characteristics, and the specific aspects investigated in interpreting and comparing research findings.

Regarding obstetric complications, our study did not find a statistically significant difference in the risk of PET between the control and case groups, which contrasts with the findings of Ruangvutilert et al., (2023) [15]. These differences may be attributed to variations in study type, population size, disease prevalence, and the specific type of thalassemia trait considered. Similarly, Leuwan et al., (2009) found no statistically significant differences in the risk of PET, APH, and polyhydramnios between cases and controls, aligning with our findings [7]. These results highlight the importance of considering context-specific factors when assessing the association between thalassemia minor and obstetric complications.

In terms of GDM, our study's findings are consistent with the research conducted by Falcone et al., (2022) [17], which reported a non-significant association between thalassemia minor and the occurrence of GDM. This indicates that thalassemia minor itself may not significantly increase the likelihood of GDM. However, the presence of both conditions may contribute to maternal and fetal complications.

An analysis done by Amooee et al., (2011) did not find significant differences in the APGAR score at one and five minutes, MSL, GDM, and PET between cases and controls [18]. However, they did report a significantly higher prevalence of CS delivery in the case group, which aligns with the findings of our study. The higher rate of CS delivery may be related to various factors, including suboptimal antenatal care and potential complications associated with thalassemia minor during pregnancy.

A finding by Hanprasertpong et al., (2013) showed no significant differences in the occurrence of GDM, preterm labor, APH, PPH, stillbirth, admission to NCU, or APGAR scores at one and five minutes [19]. These consistent findings in our study further reinforce the notion that thalassemia minor may not directly increase the risk of these specific obstetric complications. However, we did observe a significantly higher risk of postpartum hemorrhage, preterm labor, and admission to the neonatal care unit in the case group. These differences may be attributed to various factors, including the potential impact of suboptimal antenatal care received by pregnant individuals in our study, as indicated by their infrequent visits.

Interestingly, the study conducted by Wang et al.,(2023) suggested that high Hb concentration might be a trigger for GDM in Chinese pregnant women with thalassemia minor [20]. This highlights the need for further investigation into the relationship between Hb concentration and the development

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of GDM in pregnant individuals with thalassemia minor. Understanding this relationship could aid in identifying potential risk factors and implementing targeted interventions to prevent or manage GDM in this population. On the other hand, Wu et al., (2022) revealed that beta-thalassemia significantly increased the risk of polyhydramnios [21]. However, in our study, no association was found between beta-thalassemia minor and polyhydramnios. This discrepancy can be attributed to the difference in the studied populations, as their sample included diabetic pregnant individuals with thalassemia disease. The presence of comorbidities such as diabetes may influence the occurrence of polyhydramnios. This highlights the importance of considering confounding factors in the interpretation of research findings. We found a statistically significant higher rate of emergency CS, PPH, and the need for blood transfusions in the case group, aligning with the results of Koumoutsea et al., (2022) [22]. However, our findings contradict those of Leuwan et al.,(2009), which may be due to the smaller sample size in their studies [7].

Regarding neonatal outcomes, SGA, preterm labor, and the need for admission to the NCU were significantly higher in the case group. Although low APGAR score, intrapartum deaths, and IUFD were higher in some cases, the differences did not reach a significant level. Leuwan et al., (2009) found no statistically significant differences in the low APGAR score rate and perinatal mortality between the two groups, but they did find significantly higher rates of preterm labor and low birth weight in the case group [7]. Similarly, Koumoutsea et al., (2022) reported significantly higher rates of preterm labor in the case group, which aligns with our study's findings [22]. An investigation done by Amooee et al. s' study, 2011 found higher rates of preterm delivery, intrauterine growth restriction (IUGR), and low birth weight in pregnant individuals affected by beta-thalassemia minor [18]. These consistent findings across different studies provide robust evidence that thalassemia minor may contribute to impaired fetal growth and development, leading to adverse neonatal outcomes.

In comparing our study with the research conducted by Yordanova et al., (2014) we observed both similarities and differences regarding additional maternal outcomes, including IUGR, GDM, and PET. Regarding IUGR, our study found a significantly higher incidence of SGA infants in the case group, which is consistent with their findings [23]. These findings suggest that thalassemia minor may have a direct impact on fetal growth, potentially leading to growth restriction.

In terms of GDM, our study and theirs reported a non-significant association between thalassemia minor and the occurrence of GDM. This indicates that thalassemia minor itself may not significantly increase the likelihood of GDM. However, the presence of both conditions may contribute to maternal and fetal complications, as highlighted in the study by Yordanova et al. [23].

In the case group, most of the newborns who needed admission to the NCU were babies of mothers with a low mean value of Hb, a lower gestational age, a low birth weight, who had DM, oligohydramnios, MSL, were delivered by CS, and had an APGAR score < 7 at 5 minutes compared to newborns without admission to the NCU. These associations were statistically significant. These agreed with Al-Wassia et al., (2017) that found the most common cause of neonatal admission to the NCU was low birth weight, a low APGAR score at 5 min, maternal DM, premature delivery, and emergency CS [24]. Furthermore, these were similar to those found by Ismael et al., (2019) which found that the rate of admission to NCU was significantly higher in neonates of thalassemic mothers with low APGAR scores at first and five minutes and in those who delivered by CS [5]. The rate of admission to the NCU in preterm neonates and neonates of diabetic mothers was higher in the case group, which might be due to neonatal complications of diabetes and prematurity and not due to the effect of thalassemia.

However, Falcone et al., (2022) concluded that GDM is not more likely to occur in pregnant women with beta-thalassemia, but maternal and fetal complications are greater in the presence of both [17].

The outcomes of our research presented valuable opportunities for future investigations in the field of thalassemia minor and its impact on pregnancy outcomes. Further studies could explore interventions or management strategies aimed at mitigating the adverse effects associated with thalassemia minor during pregnancy. Additionally, long-term follow-up studies could assess the health and developmental impacts on offspring resulting from maternal thalassemia minor.

However, it is important to acknowledge several limitations that we encountered. Firstly, our control group was limited as we excluded Rh-negative mothers, potentially biasing the composition of the group and limiting the generalizability of our findings to the broader pregnant population. Including Rh-negative mothers in future studies would provide a more representative sample. Also, excluding fetal chromosomal abnormalities may have led to a selection bias and may have understated the frequency of these abnormalities or the link between them and maternal thalassemia.

CONCLUSION

The study provides evidence that thalassemia minor can adversely affect pregnancy outcomes and increase the frequency of neonatal admission to the NCU. The observed associations between thalassemia minor and lower Hb levels, a lower gestational age, a lower birth weight, and increased rates of obstetric and neonatal complications highlight the importance of monitoring and providing appropriate care for pregnant women with thalassemia minor. However, it is important to consider the limitations of our study and conduct further research to validate and expand upon these findings.

ETHICAL DECLARATIONS

Ethics Approval and Consent to Participate

The ethical committee had approved the protocol of the study of the Department of Obstetrics and Gynecology, College of Medicine, Kirkuk City, Iraq (document number 20 dated, December 18, 2022). All participants gave informed consent to be enrolled in the study.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

Mohammed EA was responsible for data collection and literature review. Muhammed NA was responsible for the conception and conduct of the formal analysis. Esraa EA wrote and drafted the manuscript. All authors read and approved the final version of the manuscript.

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