Maternal and Neonatal Outcomes of Syrian Adolescent Refugees and Local Adolescent Turkish Citizens: A Comparative Study at a Tertiary Care Maternity Hospital in Turkey

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ABSTRACT

OBJECTIVE: In this study, we aim to compare the maternal and obstetric outcomes between local adolescent Turkish citizens and adolescent Syrian refugees admitted to a tertiary care center in Turkey.

STUDY DESIGN: Between January 2014 and December 2019, a total of 57,049 births were performed in our hospital. The study included a total of 6,021 patients aged 19 years or younger who gave birth at our hospital. Of this number, 5,164 (1,792 Syrian adolescent refugee cases and 3,372 local adolescent Turkish cases) were live singleton pregnancies. Our primary aim was to compare the maternal and obstetric outcomes between the two groups.

RESULTS: In the pregnant refugee women, the maternal age was younger (p<0.001). Hemoglobin and hematocrit levels are significantly lower in Syrian pregnant women (p<0.001 and p<0.001, respectively). Anemia was significantly higher in Syrian refugee pregnant women (p<0.001). The double screening test and triple screening test were significantly lower in Syrian pregnant women (p<0.001 and p<0.001, respectively). Preterm birth rates and late preterm delivery prevalence (34-37 gestational weeks) were significantly higher in the adolescent Syrian immigrants compared to the adolescent Turkish locals (p<0.001 and p<0.001, respectively). The average birth weight of the Syrian refugees was lower but the number of low birth weight babies was higher Turkish locals (p=0.010 and p=0.014, respectively). The preterm birth ratio and low birth weight ratio in Syrian adolescents has decreased over the years.

CONCLUSION: Syrian adolescent refugees are particularly at risk of early pregnancy, high fertility rate, preterm birth, low birth weight, and anemia. Immigrant women should be provided with fertility, family planning, and training on behavior that protects reproductive health. Syrian pregnant women should be supported to receive services.

Keywords: Adolescent pregnancy, Antenatal care, Immigrants, Pregnancy outcome, Refugees

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Pregnant refugee women demonstrate an increased risk of adverse pregnancy outcomes such as cesarean births, preterm births, failed induction of labor, oligohydramnios, fetal distress, and gestational diabetes (5-9). Additionally, they may face malnutrition, legal problems, as well as difficulty in receiving regular antenatal care and accessing health services (5,10). The combination of these risk factors increases the risk of poor maternal and perinatal outcomes in the adolescent immigrant group.

The Syrian war started in March 2011. By May 2011, thousands of people had fled from the war to the neighboring countries, with even larger numbers displaced within Syria itself (11). Turkey is the host to the largest number of refugees all over the world (12). In July 2019, Turkey hosted over 3.6 million registered Syrian refugees (12). Approximately 6.1% of this population consists of female immigrants between the ages of 12 and 17 years (12). Izmir is an industrial city located in Western Turkey with a population of 4,320,519 people, and 3.3% of this population is Syrian refugees (12,13). The health expenditures of Syrian refugees living in Izmir are covered by the Government of the Republic of Turkey.

There are many studies in the literature on the maternal outcomes of refugees from different ethnic backgrounds and even the results of all Syrian and Turkish deliveries in our hospital were examined (14,15). However, being an adolescent is already a risky pregnancy, and considering the frequency of adolescent pregnancies in Syrian refugees, we decided to plan this study. The purpose of this study is to compare the maternal and neonatal outcomes of the Syrian immigrant adolescent pregnancies between January 2014 and December 2019 in the University of Health Sciences Tepecik Training and Research Hospital. As far as we know, this study is the adolescent refugee pregnancy study with the largest sample in Turkey.

**Material and Method**

We planned and conducted this retrospective study between January 2014 and December 2019 at the University of Health Sciences Tepecik Training and Research Hospital. This study included 6,021 patients aged 19 years or younger pregnant women who gave birth at our hospital. Of these patients, 5,164 (1,792 were Syrian adolescent refugee cases and 3,372 were local adolescent Turkish cases) were live singleton pregnancies. The study was approved by the University of Health Sciences Tepecik Training and Research Hospital Local Ethics Committee (approval number: 2019/7-10 date 25.04.2019). The research was conducted in accordance with the 1964 Helsinki Declaration. Informed consent is not required as it is a retrospective study.

All data were extracted from our hospital’s database system and patient files. Patients with chronic disease (type I and type II diabetes mellitus, heart disease, acute-chronic infectious disease, and rheumatologic disease) and twin pregnancies were not included in the study. For women who were sure of their last menstruation date, gestational age was calculated with known last menstrual period (LMP). Of the patients who did not know their last menstrual period (LMP), gestational age was calculated from crown-rump length (CRL) of first-trimester ultrasonography (US) measurements (16) (Figure 1).

![Figure 1: Pregnant women participating in the study](image_url)

In classifications; delivery at <37 weeks as preterm birth, delivery at ≥42 weeks as post-term birth, breakage of the amniotic sac before the onset of labor as premature rupture of membranes (PROM), birth weight ≥4000 grams (g) as macrosomia, and birth weight <2500 g as low birth weight (LBW) was used. Births after 28 weeks without signs of life were defined as stillbirth (17). Women who had at least two positive values in 100-g oral glucose tolerance test (OGTT) performed at 24-28 weeks of gestation were accepted as gestational diabetes mellitus (GDM) (18,19). Hemoglobin and hematocrit levels were evaluated at admission for delivery. A double screening test in the first trimester and a triple screening test in the second trimester were used for aneuploidy screening (20).

**Statistical Analysis**

The results were analyzed in the Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows. The normality distribution of variables was evaluated according to Kolmogorov-Smirnov (n>30), Shapiro-Wilk (n<30), and appropriate graphics. If the variables were parametric, a Student
t-test was used. If the variables were non-parametric, the Mann-Whitney U test was used. Chi-square and Fisher exact test were used for categorical variables and the odds ratio (95% CI) was calculated. Binary logistic regression analysis was used to determine the factors related to the cesarean section for the adolescent singleton, live pregnant women. \( p < 0.05 \) was considered significant.

**Results**

We calculated “The proportion of adolescent pregnancies according to a nationality” as the proportion of the pregnant Turkish or Syrian women who were younger than 19 years and gave birth between January 2014 and December 2019 in our clinic to the whole Turkish or Syrian women who gave birth at the same time in the same clinic. In total, there were 57,049 pregnancies, and 10.5% of them were adolescent pregnancies. The number of adolescents among the pregnant Syrian refugees in our study was 1,903 (22%), and this number was 4,118 (7%) among the pregnant Turkish women. In Syrian refugees, adolescent pregnancy is significantly higher and statistically significant \( (p < 0.001) \).

Table I shows the characteristics, along with maternal and perinatal outcomes of the participants. The age of Turkish mothers under 19 years and immigrant mothers were found to be 18 (10-19) years and 17 (10-19) years, respectively. In the Syrian refugee adolescent pregnant women, the maternal age was younger \( (p < 0.001) \). There was no statistically significant difference between the two groups with respect to multiple pregnancy rates. The rate of multiparity was higher in Syrians \( (p < 0.001) \). Hemoglobin and hematocrit levels were significantly lower in Syrians \( (p < 0.001 \) and \( p < 0.001 \), respectively), whereas anemia was significantly higher in Syrian refugee pregnant women \( (p < 0.001) \). Analysis of the delivery route revealed that cesarean rates were significantly higher for Turkish women than for Syrian refugees (42.8% vs. 25.6%, respectively). The primary cesarean rates were higher for the Turkish adolescent population as compared to the Syrian immigrants and also statistically significant \( (p < 0.001) \). In Syrian refugee pregnant women, the rates of hypertensive disorders of pregnancy and PROM were significantly lower \( (p = 0.035 \) and \( p < 0.001 \), respectively). There was no statistical difference between the two groups with respect to stillbirth, the prevalence of fetal congenital anomaly, and the number of blood transfusions (Table I).

The most common indication for elective cesarean section in Syrian and Turkish pregnant women was a previous cesarean section, whereas the indication for emergency cesarean section was fetal distress (Table II).

Table III shows the rates of antenatal parameters. The double screening test and triple screening tests were significantly lower in Syrian pregnant women \( (p < 0.001 \) and \( p < 0.001 \), respectively). However, GDM screening test rates were significantly higher in Syrian pregnant women \( (p = 0.040) \) (Table III).

### Table I: Characteristics, maternal and perinatal outcomes of pregnant Syrian and Turkish adolescents

<table>
<thead>
<tr>
<th></th>
<th>Syrian n=1792</th>
<th>Turkish n=3372</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year) median (min-max)</td>
<td>17 (10-19)</td>
<td>18 (10-19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parity (n,%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>1289 (71.9%)</td>
<td>2823 (83.7%)</td>
<td></td>
</tr>
<tr>
<td>Multiparous</td>
<td>503 (28.1%)</td>
<td>549 (16.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delivery type (n,%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>1333 (74.4%)</td>
<td>1928 (57.2%)</td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>459 (25.6%)</td>
<td>1444 (42.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cesarean Type (n,%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary C-section</td>
<td>375 (81.7%)</td>
<td>1298 (89.9%)</td>
<td></td>
</tr>
<tr>
<td>Repeated C-section</td>
<td>84 (18.3%)</td>
<td>146 (10.1%)</td>
<td></td>
</tr>
<tr>
<td>Multiple Pregnancy Prevalence (n,%)</td>
<td>20 (1.1%)</td>
<td>34 (1%)</td>
<td>0.717</td>
</tr>
<tr>
<td>Stillbirth (n,%)</td>
<td>16 (0.9%)</td>
<td>50 (1.5%)</td>
<td>0.075</td>
</tr>
<tr>
<td>Fetal Congenital Anomaly (n,%)</td>
<td>5 (0.27%)</td>
<td>11 (0.32%)</td>
<td>0.771</td>
</tr>
<tr>
<td>Hypertensive disorders of pregnancy (n,%)</td>
<td>56 (3.1%)</td>
<td>147 (4.3%)</td>
<td>0.035</td>
</tr>
<tr>
<td>PROM (n,%)</td>
<td>57 (3.2%)</td>
<td>184 (5.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb (g/dl) (mean±SD)</td>
<td>10.8±1.5</td>
<td>11.5±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematocrit (%) (mean±SD)</td>
<td>32.1±4.8</td>
<td>34.3±5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia (Hb&lt;11 (g/dl)) (n,%)</td>
<td>820 (45.7%)</td>
<td>987 (29.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood Transfusion (n,%)</td>
<td>33 (1.8%)</td>
<td>36 (1%)</td>
<td>0.078</td>
</tr>
</tbody>
</table>

*Hb: Hemoglobin, PROM: Premature rupture of membrane, SD: Standard deviation*
The prevalence of preterm birth rates and late preterm delivery (34-37 gestational weeks) was significantly higher in the adolescent Syrian immigrants as compared to the adolescent Turkish locals \((p<0.001\) and \(p<0.001\), respectively). The average birth weight of the Syrian refugees was lower but the number of LBW babies was higher in the Turkish locals \((p=0.010\) and \(p=0.014\), respectively). The number of infants with macrosomia was higher in Turkish locals \((p=0.046\)). Height and head circumference were similar in the two groups. There was no statistical difference between the two groups with respect to fetal sex, post-term delivery, and APGAR score of less than 7 at the first and fifth minutes (Table IV).

Table V presents the risk factors associated with cesarean section, which were examined by using logistic regression analysis. Accordingly, factors such as gestational age, birth weight, macrosomia, and nationality (Turkish) increased the rates of cesarean section. However, maternal age decreased the rate of cesarean section (Table V).

### Table IV: Perinatal results of all adolescent singleton and live pregnant women who participated in the study

<table>
<thead>
<tr>
<th></th>
<th>Syrian n=1756</th>
<th>Turkish n=3290</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n,%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male prevalence</td>
<td>931 (53%)</td>
<td>1692 (51.4%)</td>
<td>0.282</td>
</tr>
<tr>
<td>Female prevalence</td>
<td>825 (47%)</td>
<td>1598 (48.6%)</td>
<td></td>
</tr>
<tr>
<td>Gestational age at birth (mean±SD)</td>
<td>38±2.3</td>
<td>38.4±2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preterm Delivery Prevalence (&lt;37 weeks) (n,%)</td>
<td>377 (21.5%)</td>
<td>533 (16.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late Preterm Delivery Prevalence (34-37 weeks) (n,%)</td>
<td>295 (16.8%)</td>
<td>374 (11.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-term Delivery Prevalence (≥42 weeks) (n,%)</td>
<td>11 (0.6%)</td>
<td>35 (1.1%)</td>
<td>0.119</td>
</tr>
<tr>
<td>Birth weight (g) (mean±SD)</td>
<td>3043.3±515.4</td>
<td>3062±591.2</td>
<td>0.010</td>
</tr>
<tr>
<td>LBW (&lt;2500 g) (n,%)</td>
<td>193 (11%)</td>
<td>441 (13.4%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Head Circumference (cm) (mean±SD)</td>
<td>34±2</td>
<td>34±2</td>
<td>0.820</td>
</tr>
<tr>
<td>Height (cm) (mean±SD)</td>
<td>49.1±2.4</td>
<td>49.1±11.4</td>
<td>0.279</td>
</tr>
<tr>
<td>Macrosomia (≥4000 g) (n,%)</td>
<td>45 (2.6%)</td>
<td>118 (3.6%)</td>
<td>0.046</td>
</tr>
<tr>
<td>APGAR Score &lt;7 at 1st minute (n,%)</td>
<td>133 (7.6%)</td>
<td>312 (9.5%)</td>
<td>0.130</td>
</tr>
<tr>
<td>APGAR Score &lt;7 at 5th minute (n,%)</td>
<td>45 (2.6%)</td>
<td>66 (2%)</td>
<td>0.200</td>
</tr>
</tbody>
</table>

**LBW:** Low birth weight, **SD:** Standard deviation

### Table V: Logistic regression analysis of adolescent singleton and live pregnant women in terms of cesarean section

<table>
<thead>
<tr>
<th></th>
<th>OR 95% CI</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>0.91 (0.86-0.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>Gestational age</td>
<td>1.05 (1.01-1.08)</td>
<td>0.049</td>
</tr>
<tr>
<td>Birth weight</td>
<td>1.02 (1.01-1.03)</td>
<td>0.024</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>3.38 (2.35-4.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nationality (Turkish)</td>
<td>2.28 (2.01-2.61)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
The preterm birth ratio in Syrian adolescents has decreased over the years; it was 26.3% in 2014 and 19.5% in 2019. The LBW ratio in Syrian adolescents has decreased over the years; it was 21.1% in 2014 and 12.4% in 2019 (Figure 2). Figure 3 shows the preterm birth ratio and LBW ratio results of Turkish adolescent pregnant women (Figure 3).

**Figure 2:** The incidence of preterm delivery rate and low birth weight (LBW) rate by Syrian adolescent refugees

**Figure 3:** The incidence of preterm delivery rate and low birth weight (LBW) rate by local Turkish adolescent
Discussion

Since 2011, Turkey has come under a huge immigration wave because of the war that broke out in Syria between its government and the rebel forces (21). According to the United Nations Refugee Agency, the total number of immigration to Turkey has reached 3,629,820 in July 2019 (12). Izmir has a population of 4,320,519 people, and the number of registered Syrian immigrants in the province of Izmir, where our hospital is located, has reached 3.3% of the population residing in the province (12,13). The Syrian civil war caused the displacement of millions of Syrians, and the number of Syrian refugees giving birth in Turkey is increasing over time.

Health services for Syrians under temporary protection started when they first entered Turkey’s Hatay province on April 29, 2011. The Center for Middle Eastern Strategic Studies (ORSAM) report titled “The Effects of Syrian Refugees in Turkey 2015” states that Syrians received between 30% and 40% of total services in the state hospitals located in the border provinces. For this reason, there was a capacity problem in the state hospitals located in the border provinces (22,23). Not only refugees in Turkey, but also people living in Syria who were injured in clashes are being treated in these hospitals, and there was a capacity problem in terms of both physical conditions and health care workers. Beginning from 2011, when Syrians began to enter our country, to December 11, 2017, 31,449,800 examinations were conducted, 1,326,849 patients were hospitalized and treated, 1,112,058 Syrian patients underwent surgery, 276,158 Syrian babies were born in hospitals, and 3,215,128 doses of vaccines were administered to Syrian babies and children in accordance with the vaccination schedule (24). This dramatic increase in the immigrant population has negatively affected healthcare services. All the healthcare services are provided free of charge to the Syrian refugees. Iron and multivitamin supplementation is also free of charge to pregnant women. During pregnancy, Syrian refugee pregnant women should make antenatal visits at least four times to their family physicians.

Health services offered to pregnant women are among the most important elements of health. In this study, we compared the antenatal, obstetric, and neonatal outcomes of Syrian and Turkish adolescent pregnant women. Between January 2014 and December 2019, there were 57,049 births in our hospital. 10.5% of these births were adolescent births. High-risk pregnant women are specially referred to our hospital in our daily practice. While the number of adolescent pregnant Syrian refugees in our study was 1,903 (22%), this number was 4,118 (7%) for the pregnant Turks. Syrian refugees constitute an important part of our total patient population.

In our study, we found that the average age was lower and the adolescent birth rate was higher in the refugee pregnant women (p<0.001 and p<0.001, respectively). The mean parity number was also significantly higher in the refugee pregnant women (p<0.001). Women’s fertility is associated with many factors such as ethnicity, age, education, marriage, and socioeconomic status (25,26). The cause is often hidden in the death of one of the parents. The death of one of the parents leaves the family in grave condition. Families try to marry their daughters to ease their economic conditions (27).

The rate of preterm birth in Syrian adolescent refugee pregnant women is significantly higher (p<0.001). Problems such as inadequate antenatal care, malnutrition, insufficient iron support, social isolation, posttraumatic stress syndrome, unemployment, fear of death, and lack of education in Syrian refugee pregnant women may lead to negative pregnancy outcomes (28-32). Considering the years, while preterm birth was 26.3% in Syrian adolescents in 2014, it was 19.5% in 2019 and decreased over the years. It can be assumed that access to health services, which was much worse in the first years of the war, has slightly improved over time. The mean birth weight in Syrian refugee adolescent pregnant women was significantly lower (p<0.001). This may be due to the high number of preterm births. Also, LBW was higher in Turkish newborns (p<0.001). This phenomenon can be explained by the fact that the prevalence of late preterm delivery (34-37 gestational weeks) was higher in Syrians (p<0.001). The incidence of LBW in Turkish adolescents was 9.7% in 2014 and 14.3% in 2019. This situation parallels the slight increase in preterm delivery rates.

In the Turkish adolescent group, gestational hypertension and PROM were significantly higher than the Syrian adolescent population (p<0.001 and p<0.001, respectively). Some infectious factors (urinary tract or vagina), maternal malnutrition, low socioeconomic status, smoking, and so on are among the possible causes of premature rupture of membranes (33). While the incidence of preeclampsia and eclampsia worldwide varies between 5-26%, little is known about the varying rates in immigrant and local women (34). Increased awareness with the improvement of antenatal care improves the diagnosis of hypertension in pregnancy (35,36). Moreover, ethnicity is also a risk factor (36).

In our study, the cesarean delivery rates were significantly higher in Turkish pregnant women (p<0.001). Also, the primary cesarean section was significantly higher in the Turkish citizens in our study (p<0.001). Similarly, various researchers have also reported that the rate of deliveries by cesarean section was lower in refugees (29,37,38).

In our study, similar to some previous studies, hemoglobin and hematocrit levels in pregnant women were significantly lower and anemia rates were significantly higher in pregnant women (p<0.001, p<0.001, and p<0.001, respectively). This condition may be due to malnutrition and poor antenatal care (22,29,39).

Antenatal care is a clinical procedure for the healthy out-
come of pregnancy for mother and baby. In our country, the Ministry of Health is obliged to detect pregnancy until the 14th week and make the first follow-up. The pregnancy is to be followed at least four times until delivery. The number of follow-ups should be increased for those who are found to be at a risk for themselves or their babies. In our study, the rates of double and triple screening tests were significantly lower in the refugee pregnant women (p<0.001 and p<0.001, respectively). In a study conducted in Lebanon, the follow-ups of Syrian refugees cannot be done regularly (38). Demirci et al. reported that the antenatal follow-up of refugees was insufficient (29). Reese-Masterson et al. reported that only 51% of Syrian refugees had antenatal care with poor perinatal outcomes (39). Language differences, social isolation, and cultural differences are some of the reasons for inadequate antenatal care (5,10). Inadequate antenatal care increases maternal mortality and morbidity (38,39).

We found the rate of having a GDM screening test was higher in Syrians (p=0.040). However, we could not compare the GDM prevalence because most of the Syrian and Turkish adolescent patients did not receive GDM screening tests. The following reason can be attributed to this observation: recently, some Turkish pregnant women think that the glucose tolerance test will harm the fetus, which led to their refusal to undergo screening tests (40).

The prevalence of APGAR score of less than 7 at the first and fifth minute was similar between the groups. This may be because the late preterm delivery rates of the Syrians are higher despite all the bad conditions. Also, the results are similar to those of Turkay et al.(41).

The logistic regression analysis performed in the whole adolescent group revealed that gestational age, birth weight, macrosomia, and being an adolescent Turkish citizen significantly increased the cesarean rates. Moreover, maternal age has decreased the cesarean rates.

The limitations of our study: Retrospective study is the most important limitation of our study and we could not access some data because it was. The data in our hospital, which is a tertiary center, may not reflect the whole Syrian group. For this reason, multicenter prospective studies are needed.

The strengths of our study: Our study is a large sample study that examines the maternal-obstetric results of pregnant immigrant adolescents and pregnant local adolescents.

**Conclusion**

There are significant differences between Turkish and refugee adolescent pregnant women. Antenatal follow-up of refugee pregnant women is not enough. Syrian refugees are particularly at risk for adolescent early pregnancy, high fertility rate, preterm birth, LBW, and anemia. Immigrant women should be provided with fertility, family planning, and training on behavior that protects reproductive health. Syrian pregnant women should be supported to receive services. It would be useful to have an interpreter in clinics.

**Acknowledgment:** None

**Competing interests:** The authors declare that they have no competing interests.

**Funding:** The authors received no funding for this work.

**Ethics approval and consent to participate:** Informed consent is not required as it is a retrospective study. The study was reviewed and approved by the ethics committee of the University of Health Sciences Tepecik Training and Research Hospital (approval number: 2019/7-10 date 25.04.2019). All procedures were performed according to the Declaration of Helsinki.

**Availability of data and materials:** The data supporting this study is available through the corresponding author upon reasonable request.

**Authors’ contributions:** CG conducted the population study, analyzed and interpreted the data, and drafted the manuscript. BB participated in data analysis, interpretation, and draft revision. TV and HG participated in data collection and result interpretation. TV, HG, AGSY assisted with data collection and analysis. All authors read and approved the final manuscript.

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