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ANALYSIS OF THE EFFECTIVENESS OF FIRST TRIMESTER NUCAL TRANSLUCENCE, FREE BETA-HUMAN CHORIONIC GONADOTROPIN, AND PREGNANCY-RELATED PLASMA PROTEIN-A IN PREDICTION OF PREGNANCY COMPLICATIONS

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Abstract: In this study, we aimed to investigate whether there was an association between fetal nuchal translucency (NT) and the serum markers plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (β-hCG) measured by the first-trimester screening test, as well as birth weight and hypertension. 454 pregnant women who had undergone the first-trimester screening test for Down syndrome were included in the study. All measurements and values of NT, PAPP-A and β-hCG levels were performed between gestational weeks 11-14. Values of PAPP-A and β-hCG converted to multiples of the corrected median (MoM) were obtained using the PRISCA software package. Regarding the prediction of SGA infants, when the PAPP-A value < was 0.99MoM as a threshold, and when the free β-hCG value < was 0.69 MoM, SGA cases could be detected with a sensitivity of 83% and a specificity of 71.9%. Regarding the prediction of hypertension, at a threshold PAPP-A value of <of 0.96 MoM, cases of hypertension could be detected with a sensitivity of 70% and a specificity of 74%. Maternal PAPP-A level in the first trimester was found to correlate with neonatal birth weight (rho: 0.56 (95% CI 0.49-0.62), P < 0.0001), while β-hCG showed a weak but significant correlation with birth weight (rho: 0.137 (95% CI 0.045.) -0.227), P: 0.0036). Low PAPP-A levels in the first trimester were an effective predictor of SGA babies and hypertension, while low β-hCG levels were an effective predictor of SGA babies. There is a significant correlation between first trimester PAPP-A and β-hCG levels and birth weight.

Keywords: First trimester, NT, PAPP-A, β-hCG, Birth weight, Preeclampsia

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1. Introduction

The perinatal mortality rate and the maternal mortality rate are reliable measures of the health status of a society. One of the tests used in prenatal follow-up is the first trimester Down syndrome screening test. Using fetal nuchal translucency (NT) measured at 11-13 6/7 weeks of gestation and levels of free beta-human chorionic gonadotropin (free βHCG) and pregnancy-associated plasma protein-A (PAPP-A) measured in maternal serum, trisomy 21 has been found with 90% accuracy and a false-positive rate of 5% (Kapustin et al., 2022). In the literature, there are associations between low maternal serum-free βHCG and PAPP-A levels in the first trimester and pregnancies with preeclampsia and fetal growth retardation. Increased nuchal thickness is also associated with poor prognosis (Hughes et al., 2019). In this study, we aimed to identify pregnant women who might develop complications in the early stages by using NT measurement and biochemical markers as part of the first-trimester screening test for Down syndrome (Espid et al., 2021)

2. Materials and Methods

This study was designed retrospectively. 618 pregnant women were included in the study who underwent first-trimester screening at the Department of Obstetrics and Gynecology, Haseki Training and Research Hospital, between January 2010 and April 2011. Each patient's 11-14-week screening was performed by a board-certified specialist using a Logic 400 Pro series ultrasound machine (General Electric, USA) via an abdominal transducer. Maternal age was expressed in days, months,

and years. The number of gravidities, parity, abortion, preterm birth, and live infants were questioned and also recorded. Weeks of gestation were calculated separately according to the mother's last menstrual period and the crown-rumb length of the fetus (CRL) (DASCAU et al., 2020). Biometric evaluation of the fetus; was done with CRL measurements (Figure 1).

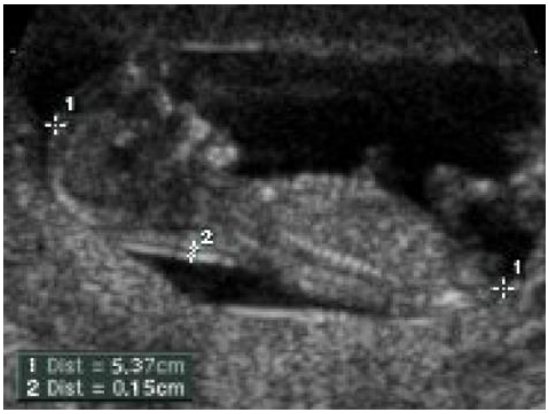

Figure 1. The crown-rumb length of the fetus measurement.

CRL was performed in the neutral position by measuring the distance between the cranial and caudal ends of the fetal body in the sagittal plane. Then, the fetal profile was determined in the neutral position in the sagittal plane. Free β-hCG and PAPP-A were examined with the Immulite 2000 in our lab. Free β-hCG was determined by the chemiluminescence immunoassay method, and for PAPP-A, the enzyme-labelled chemiluminescence immunoassay method was used (Hoseini et al., 2020). PAPP-A and Free-β-hCG values measured with the DPC kits are converted to the corrected multiple of median (MoM) values using the PRISCA software package. Preterm births are births that occurred before 37 weeks. Birth before 24 weeks gestation and below was defined as abortion (Ziolkowska et al., 2019). A systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg after 20 weeks' gestation was considered pregnancy-induced hypertension. Babies with birth weights below the 3rd percentile were defined as intrauterine growth retardation (IUGR).

2.1. Statistical Analysis

Statistical significance was examined by analyzing the results with the Medcalc program. Linear regression analysis was performed by matching the value CRL with the week of pregnancy. Indicator values and pregnancy outcomes of cases in the groups with complications were compared using Fisher's exact test, chi-square test, and Student t-test. The effectiveness of maternal serum PAPP-A and Free-β-hCG levels in predicting pregnancy complications was evaluated by Roc curve analysis. The relationship between marker levels and birth weight was determined by the Spearman correlation coefficient. The P value < 0.05 was considered significant.

3. Results

Our study included 454 mothers who were examined in the perinatology clinic at 11-14 weeks of age and were found to have no major abnormalities. The fetal nuchal translucency (NT) percentiles calculated by weeks of gestation are present Table 1. In 618 cases (73.46%), the mothers called by phone for information. The mean age of the 454 patients was 27.14±4.8 years. The mean number of pregnancies was 2.33±1.3; 185 (40%) of the patients were nulliparous. During the study, the mean week of pregnancy was 12.68±0.6. The mean value of the performed CRL measurements was 65.7±8.2 mm. Regression analysis of the relationship between NT and CRL showed significance, the regression equation NT: 0.54+0.016×CRL, r^2=0.18, P < 0.001. This points first-degree correlation between CRL and NT (Figure 2).

Table 1. The fetal nuchal translucency (NT) percentiles calculated by weeks of gestation

GW	5. per.	10. per.	25. per.	50. per.	75. per.	90. per.	95. per.
11+6-12+6 (n:175)	1.2	1.2	1.3	1.49	1.6	1.8	2.1
13-13+6 (n:244)	1.2	1.3	1.5	1.67	1.8	2.0	2.13
14-14+1 (n:35)	1.4	1.4	1.62	1.78	2.0	2.0	2.07

GW= gestational weeks

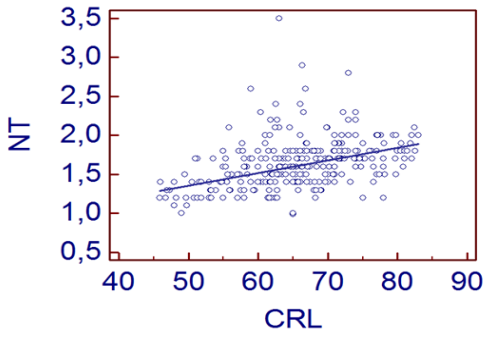

Figure 2. The fetal nuchal translucency (NT) values are measured according to CRL data.

In the second trimester, an anomaly was found in three cases. Cardiac anomaly (CRL: 62.5mm, NT:2.4), spina bifida-hydrocephalus (CRL: 60mm, NT:1.6), hydrocephalus (CRL: 55mm, NT:1.2). The patient with cardiac anomaly was included in the high-risk group because the NT value was at the > 95th percentile. Delivery occurred in these cases. Twenty-eight cases (6.1%) have a NT value of ≥2.1 (95th percentile) and above. The pregnancy outcomes of these cases were compared with normal NT thickness cases (< 95th percentile), and there was no significance. (Table 2).

Data from those born small for gestational age were

compared with those born normal or large for gestational age. Mean PAPP-A and β-hCG MoM levels were significantly lower in SGA cases. The rate of hypertensive cases was also significantly higher in this group (Table 3). Hypertensive cases compared to normotensive cases, the birth week and birth weight were significantly lower in the hypertensive cases. The mean maternal serum PAPP-A MoM level was significantly lower in hypertensive infants (Table 4).

Table 2. Comparison of cases with increased nuchal thickness and newborn outcomes of normal ones.

	NT ≥2.1mm (n:28)	NT<2.1mm (n:426)	P value
Anomaly(n)	1(%3.57)	2(%0.46)	0.44
SGA (n)	3(%10.7)	86(%20.18)	0.32
Hypertensive (n)	9(%32.14)	80(%18.77)	0.13
week of birth (Week±SD)	37.6±3.3	38.3±2	0.088
Premature Birth (n)	5(%17.8)	45(%10.5)	0.37
Birth weight (Grams±SD)	3192±790	3089±577	0.37
Birth by cesarean (n)	10(%35.7)	196(%46)	0.38

NT= fetal nuchal translucency, SGA= small for gestational age

Table 3. Demographic findings of SGA cases and comparison of first-trimester screening test results and newborn results of AGA-LGA cases.

	SGA (n:89)	AGA- LGA (n:365)	P value
Maternal Age (year±SD)	27.5±4.2	27±4.94	0.37
Gestational week (week±SD)	12.8±0.67	12.65±0.58	0.034
Mean NT (mm±SD)	1.58±0.27	1.61±0.31	0.4
Mean PAPP-A (MoM±SD)	0.82±0.37	1.64±0.97	<0.0001
Mean β-hCG (MoM±SD)	0.9±0.7	1.31±0.8	<0.0001
Birth week (week±SD)	38.14±1.96	38.35±2.2	0.4
Birth weight (gram±SD)	2422±356	3263±515	<0.0001
Hypertensive (n)	35(%39.3)	54(%14.7)	<0.0001

SGA= small for gestational age, AGA= appropriate for gestational age, LGA= large for gestational age, NT= fetal nuchal translucency, PAPP-A= plasma protein-a, β-hCG= free beta-human chorionic gonadotropin, MoM= multiples of the corrected median, SD= standard deviation.

Table 4. Comparison of demographic data and newborn outcomes of hypertensive cases with normotensives

	Hypertensive(n:89)	Normotensive(n:365)	P value
Maternal Age (year±SD)	27.6±4.68	27±4.84	0.29
Gestational week (week±SD)	12.96±0.6	12.6±0.59	<0.0001
Mean NT (mm±Sd)	1.67±0.32	1.59±0.3	0.026
Mean PAPP-A (MoM±SD)	0.99±0.65	1.6±0.96	<0.0001
Mean β-hCG (MoM±SD)	1.21±0.92	1.23±0.76	0.83
Birth week (week±SD)	36.5±3.1	38.7±1.56	<0.0001
Birth Weight (gram±SD)	2498±635	3244±477	<0.0001
SGA(n)	35(%39.3)	54(%14.79)	<0.0001

NT= fetal nuchal translucency, PAPP-A= plasma protein-a, β-hCG= free beta-human chorionic gonadotropin, SGA= small for gestational age, MoM= multiples of the corrected median, SD= standard deviation.

The effectiveness of the PAPP-A value in predicting SGA babies was evaluated with the Roc curve. When the cut-off value was < 0.99MoM, SGA cases could be detected with a sensitivity of 83% and a specificity of 71.9% (Figure 3). When the threshold < was 0.69 MoM, SGA cases could be detected with a sensitivity of 57% and a specificity of 77% (Figure 4).

The efficacy of PAPP-A level in predicting hypertension was evaluated by Roc curve. When the threshold < was 0.96 MoM, hypertensive cases could be detected with a sensitivity of 70% and a specificity of 74% (Figure 5). The efficiency of the free beta HCG value in predicting

hypertension was evaluated with the Roc curve. When the threshold < was 0.68 MoM, hypertensive cases could be detected with a sensitivity of 42% and a specificity of 76% (Figure 6). Maternal PAPP-A correlates with neonatal birth weight in the first trimester (rho: 0.56 (95% CI 0.49-0.62), P < 0.0001), whereas free beta HCG showed a weak but significant correlation with birth weight (rho: 0.137 (95% CI 0.045.) -0.227), P:0.0036) (Figures 7 and 8).

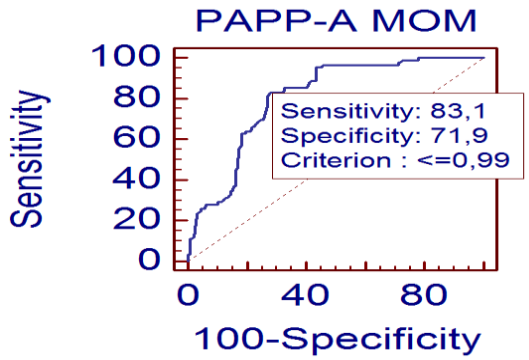

Figure 3. Roc curve evaluating the efficiency of maternal PAPP-A level in predicting SGA (AUC: 0.8, standard error: 0.022, P < 0.0001). The efficiency of β-hCG value in predicting SGA babies was evaluated by Roc curve.

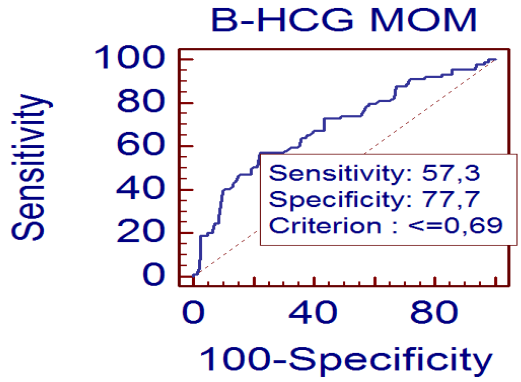

Figure 4. Roc curve evaluating the efficacy of maternal β-hCG level in predicting SGA (AUC: 0.69, standard error: 0.032, P < 0.0001).

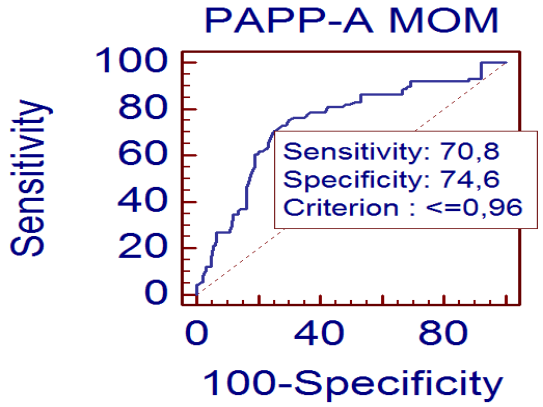

Figure 5. Roc curve evaluating the efficacy of maternal PAPP-A level in predicting hypertension (AUC: 0.74, standard error: 0.03, P < 0.0001).

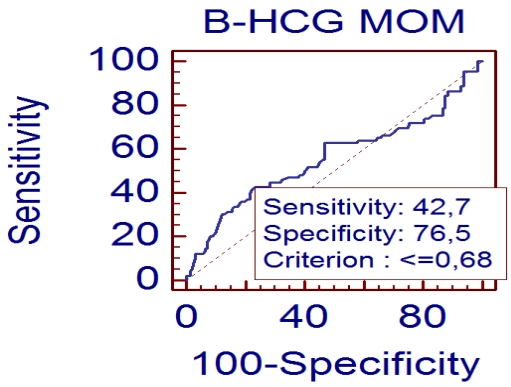

Figure 6. Roc curve evaluating the effectiveness of maternal β-hCG value in the prediction of hypertension (AUC: 0.55, Standard error: 0.038, P: 0.135).

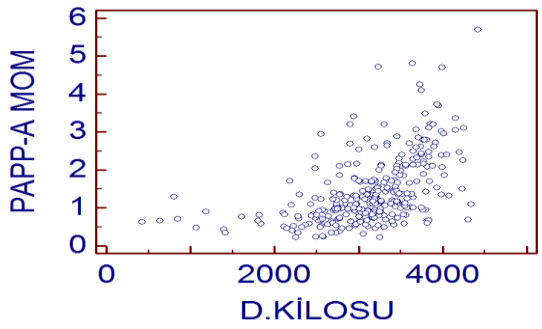

Figure 7. Maternal PAPP-A values and distribution of birth weights.

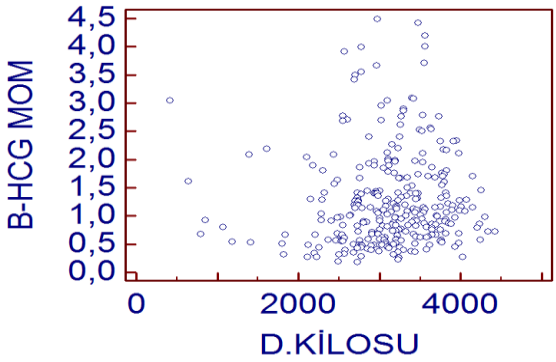

Figure 8. Distribution of maternal β-hCG values and birth weights

Roc curve analysis showed that low PAPP-A in the first trimester was a good predictor of SGA babies and hypertension (Boutin et al., 2018). It was found that a low free beta HCG value may be a good predictor of SGA babies. The efficacy of different biochemical marker values in relation to SGA birth weight or prediction of pregnancy-induced hypertension is shown in Tables 5 and 6.

Table 5. Efficiency of various values of biochemical markers in Prediction of SGA infants

	Sensitivity (%)	Specificity (%)	+LR	-LR
PAPP-A <0.37 MoM	11.24	99.16	13.45	0.9
<0.58 MoM	28.09	93.87	4.58	0.77
<0.99 MoM	83.15	71.87	2.96	0.23
β-hCG <0.37 MoM	19.1	94.99	3.81	0.85
<0.5 MoM	40.45	89.42	3.82	0.67
<0.69 MoM	57.3	77.72	2.57	0.55

PAPP-A= plasma protein-a, β-hCG= free beta-human chorionic gonadotropin, SGA= small for gestational age, MoM= multiples of the corrected median.

Table 6. Efficiency of various values of biochemical markers in the prediction of pregnancy-induced hypertension

	Sensitivity (%)	Specificity (%)	+LR	-LR
PAPP-A <0.37 MoM	5.62	97.77	2.51	0.97
<0.58 MoM	26.97	93.58	4.2	0.78
<0.96 MoM	70.79	74.58	2.78	0.39
β-hCG <0.37 MoM	13.48	93.58	2.1	0.92
<0.5 MoM	30.34	86.87	2.31	0.8
<68 MoM	42.7	76.54	1.82	0.75

PAPP-A= plasma protein-a, β-hCG= free beta-human chorionic gonadotropin, SGA= small for gestational age, MoM= multiples of the corrected median.

4. Discussion

Preeclampsia is associated with significant risks for the fetus and the mother. It is among the leading causes of perinatal mortality and morbidity (Livrinova et al., 2019). Recent studies have shown that NT and biochemical markers in the first trimester of Down syndrome screening test; that it is associated with fetal weight and height at the time of delivery and pregnancy complications such as preterm birth, miscarriage, stillbirth, and pregnancy-related hypertension (Rathakrishnan 2022).

In our study, PAPP-A was found to be significantly lower in the hypertensive group, but there was no significant difference in free β-hCG between the hypertensive and normotensive groups. When 0.96 MOM was taken as the threshold for PAPP-A, the sensitivity was determined to be 70%. PAPP-A could be a parameter to predict the pregnant women who may develop hypertension (Kim et al., 2021).

In the literature, the study by Hendrix et al., compared the biochemical markers of the first-trimester screening test of 222 pregnant women with preeclampsia and 47,770 control cases. Similar to our study, a significantly lower PAPP-A level was found in the patient group, whereas there was no significant difference in free β-hCG between the two groups (Hendrix et al., 2019).

When the threshold for PAPP-A was 0.41 MOM, the detection rate of preeclampsia was 14.6%. In our study, cases born small for their gestational age were compared with those born normal or large. The mean PAPP-A level was significantly lower in SGA cases (Shah et al., 2020). The mean free β-hCG level was also low in this group, but the difference was not significant.

Dieste-Pérez et al.evaluated the relationship between first-trimester maternal serum free β-hCG and PAPP-A levels and pregnancy complications in 5297 pregnant women, 80 of whom were preeclamptic; PAPP-A and free β-hCG were significantly lower in the preeclamptic group than in the control group (Dieste-Pérez et al., 2022).

It was found that 10% of preeclamptic pregnant women had PAPP-A levels below the 5th percentile and 7% of them had free β-hCG levels below the 5th percentile (Hu et al., 2020) Hendrix et al. (2021) studied 8839 pregnant women, of whom 331 were preeclamptic. Similar to our study, the PAPP-A level was significantly lower in the preeclampsia group, whereas free β-hCG did not make a significant difference between the two groups.

The risk of preeclampsia has been found to be increased in pregnant women with a PAPP-A score below the 5th percentile. In a study of 878 pregnant women ,it was shown that a PAPP-A value of ≤ 0.5 MoM (10th percentile) predicted 1/3 of women developing SGA (Livrinova et al., 2018). It was also found that the PAPP-A level is not an independent risk factor for preeclampsia. Bouariu et al included 2200 pregnant women in their study. PAPP-A levels were not only determined at standard weeks 10-14 but corrected PAPP-A MoM levels were also calculated (Bouariu et al., 2022)

Patients who developed preeclampsia, severe PIH, spontaneous pregnancy loss, or SGA were included in the case group and compared with the control group. When screening for poor pregnancy outcomes, the sensitivity was 38.7%, the specificity was 81.6%, and the PAPP-A threshold was ≤0.4 MoM.

The risk of fetal loss, preeclampsia, and SGA development was found to be twofold higher in women with low PAPP-A in early pregnancy. In the study involving 4390 pregnant women, it was found that the mean PAPP-A value measured at 11-13+6 weeks of gestation was significantly lower and the mean uterine artery value PI, measured at 22-24 weeks of gestation, was significantly higher in the group with preeclampsia and fetal growth retardation. It was found that there was no significant difference between free β-hCG MoM levels (Noël et al., 2021).

In another study,289 pregnant women whose PAPP-A was considered low at first-trimester screening (< 0.4 MoM). In these pregnant women, the predictive value of uterine artery Doppler performed at 18 and 22 weeks gestation was compared (Papastefanou et al., 2021). While uterine artery Doppler performed at 18 weeks gestation does not predict low birth weight, preeclampsia, or preterm birth, uterine artery Doppler performed at 22 weeks gestation has been shown to significantly predict it (Chandramohan et al., 2021). In our study, no significant difference was found between the pregnancy outcomes and neonatal findings of the cases with a NT measurement ≥2.1 (95th percentile) and above with the cases with normal NT thickness (< 95th percentile).

The first-trimester screening test is now performed in many centers. The use of the same test for preeclampsia screening provides a simple and cost-effective way to identify the population at risk for preeclampsia since the results are available at the end of the first trimester and close monitoring of pregnant women at risk and appropriate treatment will reduce fetomaternal complications. Investigating and explaining the association between pregnancy complications may also elucidate the etiology of some pregnancy complications.

5. Conclusion

In our study, it was found that the NT value increased with the week of pregnancy. It was found that the thickness of NT was not a determining factor for the outcome of pregnancy and neonatal findings. As a result of the study, it was found that a low PAPP-A value in the first trimester was effective in predicting SGA babies and hypertension; it was found that a low β-hCG value may be effective in predicting SGA babies. It was found that there was a significant correlation between first trimester PAPP-A and β-hCG levels and birth weight.

Conflict of interest

The authors declared that there was no potential conflict of interest related to the research, authorship, and/or publication of this article.

Ethical Approval/Informed Consent

The Clinical Research Ethics Committee of Haseki Research and Teaching Hospital approved this study (approval number 47 and date 11/10/13), and all patients gave written informed consent to participate in all procedures associated with the study.

Author Contributions

Concept: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Design: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Supervision: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Data collection and/or processing: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Data analysis and/or interpretation: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Literature search: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Writing: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Critical review: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Submission and revision K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%). All authors reviewed and approved final version of the manuscript.

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