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Second- to third-trimester longitudinal growth assessment for prediction of small-for-gestational age and late fetal growth restriction

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KEYWORDS: fetal growth; fetal growth restriction; longitudinal growth; small-for-gestational age; ultrasound

ABSTRACT

Objective *Detection of fetal growth restriction (FGR) remains poor and most screening strategies rely on cross-sectional evaluation of fetal size during the third trimester. A longitudinal and individualized approach has been proposed as an alternative method of evaluation. The aim of this study was to compare second- to third-trimester longitudinal growth assessment to cross-sectional evaluation in the third trimester for the prediction of small-for-gestational age (SGA) and late FGR in low-risk singleton pregnancy.*

Methods *This was a prospective cohort study of 2696 unselected consecutive low-risk singleton pregnancies scanned at 21 ± 2 and 32 ± 2 weeks. For cross-sectional growth assessment, abdominal circumference (AC) measurements were transformed to z-values according the 21st-INTERGROWTH standards. Longitudinal growth assessment was performed by calculating the AC z-velocity and the second- to third-trimester AC conditional growth centile. Longitudinal assessment was compared with cross-sectional assessment at 32 weeks. Association of cross-sectional and longitudinal evaluations with SGA and late FGR was assessed by logistic regression analysis. Predictive performance was determined by receiver–operating characteristics curve analysis.*

Result *In total, 210 (7.8%) newborns were classified as SGA and 103 (3.8%) as late FGR. Neither longitudinal measurement improved the association with SGA or late FGR provided by cross-sectional evaluation of AC z-score at 32 weeks. Areas under the curves of AC z-velocity and conditional AC growth were significantly smaller than those of cross-sectional AC z-scores (*$P < 0.001$*), although AC z-velocity performed significantly better than did conditional AC growth (*$P < 0.001$*).*

Conclusion *Longitudinal assessment of fetal growth from the second to third trimester has a low predictive capacity for SGA and late FGR in low-risk singleton pregnancy compared with cross-sectional growth evaluation. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Fetal growth assessment is a cornerstone of routine prenatal care[1]. In about 10% of pregnancies, fetal growth is lower than expected[2], with most of these cases corresponding to 'constitutionally' small-for-gestational age (SGA), healthy fetuses. However, a fraction of these present with a pathological growth pattern also known as fetal growth restriction (FGR). This condition is associated with deficient placental function, worse perinatal outcome and higher rates of long-term cardiovascular and metabolic diseases[3–5].

FGR presents as two phenotypes: early FGR (detected < 32 weeks), which is strongly related to placental insufficiency and linked to most cases of morbidity and mortality, and late FGR (detected > 32 weeks), which is characterized by a milder and near-term presentation[6]. Early diagnosis and classification define management and prognosis[6,7]; while the main challenge in early FGR is management, in late FGR it is detection. Indeed, non-detection of FGR confers an increased risk of adverse perinatal outcome[8] and stillbirth[9].

Despite implementation of screening strategies and wide availability of ultrasound, at least 30% of

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growth-restricted fetuses are not detected as such before delivery[2,3,10–12]. Most screening strategies rely on cross-sectional evaluation of fetal size (usually abdominal circumference (AC) or estimated fetal weight (EFW)) during the third trimester. It could be argued that such strategies are likely to yield suboptimal performance because they fail to capture the dynamics of fetal growth by considering FGR as a point event rather than a process. It has been proposed that this limitation could be overcome by longitudinal (serial) assessment, which would allow a more appropriate evaluation of time-dependent changes[13]. In the first half of pregnancy, decreased growth velocity is already associated with an increased risk of perinatal mortality[14]. Similarly, during the second half of pregnancy, longitudinal growth assessment seems to improve prenatal characterization of at-risk fetuses by differentiating those that present a worse perinatal outcome[10,15,16]. The extent to which this could be translated into low-risk pregnancy is largely unknown.

The aim of the present study was to compare second- to third-trimester longitudinal growth assessment to cross-sectional evaluation in the third trimester in the prediction of SGA and late FGR in low-risk pregnancy.

METHODS

Study design and participants

Between October 2006 and October 2012, a prospective cohort of unselected consecutive singleton pregnancies was constructed, each attending the Department of Maternal-Fetal Medicine in the Hospital Clinic of Barcelona for routine second- (21 ± 2 weeks) and third- (32 ± 2 weeks) trimester scans. Gestational age was calculated by measurement of crown–rump length in the first trimester[17]. Exclusion criteria were: chromosomal anomalies confirmed by genetic approaches (conventional karyotyping or array-comparative genomic hybridization), structural defects suspected at the time of routine scans and confirmed postnatally, evidence of fetal infection confirmed by microbiological examination in maternal blood and/or amniotic fluid and suspected early FGR (ultrasound EFW $< 10^{th}$ centile, according to local standards[18]) or pre-eclampsia before 32 weeks. The local Ethics Committee approved the research (HCP 2006/3204) and each patient gave written informed consent. The study design, analysis and reporting adhered to the STARD recommendations[19].

Measurements

At 21 ± 2 and 32 ± 2 weeks' gestation, ultrasound scans were performed by certified ultrasonologists using ultrasound machines equipped with 6–2-MHz linear curved-array transducers. The following biometric measurements were obtained at each scan, adhering to standardized recommendations[20]: biparietal diameter (measured in the transverse plane at the level of the thalami and the cavum septi pellucidi, from the outer to inner border of the skull), head circumference (in the same plane as that of the biparietal diameter, with ellipse placement outside of the skull bones), AC (transverse section of the abdomen at the level of the portal sinus and stomach, with ellipse placement on the outer surface) and femur length (longest length of the ossified diaphysis). EFW was calculated from these four parameters using the Hadlock formula[21].

Outcomes

SGA was defined as birth weight below the 10^{th} centile, according to customized standards[18]. Late FGR was defined as birth weight below the 3^{rd} centile or below the 10^{th} centile in the presence of abnormal uterine artery Doppler (pulsatility index $> 95^{th}$ centile[22]) or abnormal cerebroplacental ratio ($< 5^{th}$ centile[23]) within 1 week prior to delivery.

Pre-eclampsia was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy[24].

Adverse perinatal outcome was defined as stillbirth, presence of non-reassuring fetal status requiring emergency Cesarean section, 5-min Apgar score < 7 or neonatal metabolic acidosis at birth, defined as the presence of umbilical artery pH ≤ 7.15 and base excess > 12 mEq/L at birth.

Statistical analysis

One-way ANOVA (with polynomial contrast for linear trends) and Pearson's chi-square test (with linear-by-linear test for linear trends) were performed for univariate comparisons between non-SGA, SGA and late FGR maternal and pregnancy characteristics for quantitative and qualitative variables, respectively.

For cross-sectional growth assessment, AC measurements were transformed to *z*-values (AC *z*-score) according the 21st-INTERGROWTH standards[11].

Longitudinal growth assessment was performed by calculating: (1) AC *z*-velocity[25] = (AC *z*-score in third trimester – AC *z*-score in second trimester)/interval between scans (days) and (2) second- to third-trimester conditional growth centile[26], allowing quantification of an observed AC measurement in the third trimester given the value expected from a second-trimester measurement (conditional AC).

The association of longitudinal growth with SGA and late FGR was assessed by logistic regression, in which the basal model for comparison was the cross-sectional evaluation in the third trimester. Models were compared by assessing the improvement in their Naegelkerke R^2 as a measure of goodness-of-fit, i.e. the proportion of uncertainty explained by the model. A clinically relevant improvement in the model performance was defined by an increase in R^2 of >10%.

The performance of prediction of SGA and late FGR was determined by receiver–operating characteristics (ROC) curve analysis. Paired ROC curves were compared

by the De Long method[27]. Probability values < 0.05 were considered statistically significant.

All statistical analyses and graph constructions were performed with open source software R version 2.15.1 (The R Foundation for Statistical Computing) with the package pROC version 1.7.2.

RESULTS

In total, 2757 patients met the inclusion criteria and were evaluated at 21 ± 2 weeks' gestation. Of them, 32 were lost to follow-up, 22 were diagnosed with early pre-eclampsia or FGR before a routine third-trimester scan, four were excluded for congenital anomalies and three for chorioamnionitis. Therefore, 2696 patients were included in the analysis.

In total, 210 (7.8%) newborns qualified as SGA and 103 (3.8%) as late FGR. Of the late FGR group, 59 (57.3%) had a birth weight lower than the 3rd centile, 35 (34.0%) had an abnormal cerebroplacental ratio and 29 (28.2%) had abnormal uterine artery Doppler; these incidences were not mutually exclusive. The characteristics of the study population are given in Table 1. Compared with SGA patients, those with late FGR had higher rates of white European ethnicity ($P = 0.002$), smoking ($P < 0.001$), previous adverse perinatal outcome ($P = 0.014$) and pre-eclampsia ($P < 0.001$).

Table 2 shows logistic regression models for the association of SGA and late FGR with AC *z*-score, AC *z*-score plus AC *z*-velocity and AC *z*-score plus conditional AC. Of note, the AC *z*-velocity and the conditional AC were independently and significantly associated with SGA ($P = 0.004$ and $P = 0.027$, respectively) but not with

Table 1 Maternal and pregnancy characteristics of cohort of 2696 low-risk singleton pregnancies, according to outcome

Characteristic	*Non-SGA* (n = *2383*)	*SGA* (n = *210*)	*Late FGR* (n = *103*)	P*	P†
Age (years)	31.6 ± 5.3	31.9 ± 5.8	31.8 ± 5.2	0.768	0.578
BMI (kg/m^2) at booking	23.9 ± 3.7	23.7 ± 4.0	22.9 ± 3.1	0.024	0.011
GA at 21-week ultrasound (weeks)	21.1 ± 0.8	21.0 ± 0.7	21.1 ± 0.7	0.994	0.967
GA at 32-week ultrasound (weeks)	33.0 ± 0.7	33.0 ± 0.7	32.6 ± 1.0	< 0.001	< 0.001
GA at delivery (weeks)	39.8 ± 1.5	39.8 ± 1.7	37.4 ± 2.8	< 0.001	< 0.001
White European ethnicity	1429 (60)	137 (65.2)	85 (82.5)	< 0.001	< 0.001
Low socioeconomic level	1001 (42)	106 (50.5)	61 (59.2)	< 0.001	< 0.001
Nulliparity	1412 (59.3)	150 (71.4)	73 (70.9)	< 0.001	< 0.001
Smoking	286 (12)	35 (16.7)	46 (44.7)	< 0.001	< 0.001
Previous adverse perinatal outcome‡	45 (1.9)	9 (4.3)	12 (11.7)	< 0.001	< 0.001
Maternal disease§	356 (14.9)	37 (17.6)	15 (14.6)	0.575	0.633
Pre-eclampsia	54 (2.3)	14 (6.7)	23 (22.3)	< 0.001	< 0.001
Adverse perinatal outcome	331 (13.9)	57 (27.1)	25 (24.3)	< 0.001	< 0.001
Emergency CS for NRFS	164/2240 (7.3)	33/202 (16.3)	15/85 (17.6)	< 0.001	< 0.001
5-min Apgar score < 7	8 (0.3)	0 (0)	1 (1)	0.375	0.654
Neonatal acidosis	208/2228 (9.3)	33/191 (17.3)	13/93 (14)	0.001	0.002
NICU admission	2 (0.1)	0 (0)	0 (0)	0.877	0.631
Stillbirth	2 (0.1)	0 (0)	1 (1)	0.027	0.051

Data are given as mean ± SD, *n* (%) or *n*/*N* (%). Statistical significance set at $P < 0.05$. *One-way ANOVA or Pearson chi-square test as appropriate. †Polynomial contrast or linear-by-linear test for linear trends. ‡Previous adverse perinatal outcome: previous pre-eclampsia, FGR or stillbirth. §Maternal disease: chronic hypertension, diabetes mellitus, renal disease, autoimmune disease, coagulation disorders, neurologic disease, psychiatric disease, thyroid disease or HIV. BMI, body mass index; CS, Cesarean section; FGR, fetal growth restriction; GA, gestational age; NICU, neonatal intensive care unit; NRFS, non-reassuring fetal status; SGA, small-for-gestational age.

Table 2 Logistic regression models for association of cross-sectional (abdominal circumference (AC) *z*-score) and longitudinal (AC *z*-velocity and conditional AC) parameters with small-for-gestational age (SGA; $n = 210$) and late fetal growth restriction (FGR; $n = 103$) in a cohort of 2696 singleton pregnancies

Outcome	*Model*	*Naegelkerke* R^2	*Parameter*	β	*Odds ratio (95% CI)*	P
SGA	AC *z*-score	0.224	AC *z*-score	−1.31	0.27 (0.23–0.32)	< 0.001
	AC *z*-score plus AC *z*-velocity	0.23	AC *z*-score	−1.43	0.24 (0.20–0.29)	< 0.001
			AC *z*-velocity	0.20	1.22 (1.07–1.39)	0.004
	AC *z*-score plus conditional AC	0.228	AC *z*-score	−1.36	0.26 (0.22–0.31)	< 0.001
			Conditional AC	0.01	1.01 (1.00–1.01)	0.027
Late FGR	AC *z*-score	0.402	AC *z*-score	−2.18	0.11 (0.08–0.16)	< 0.001
	AC *z*-score plus AC *z*-velocity	0.405	AC *z*-score	−2.29	0.10 (0.07–0.15)	< 0.001
			AC *z*-velocity	0.18	1.19 (0.94–1.51)	0.147
	AC *z*-score plus conditional AC	0.402	AC *z*-score	−2.18	0.11 (0.08–0.16)	< 0.001
			Conditional AC	0.00	1.00 (0.99–1.01)	0.96

AC *z*-score measurements taken at 32 weeks' gestation. AC *z*-velocity and conditional AC measurements taken at 21 and 32 weeks' gestation.

late FGR. However, although longitudinal assessment significantly improved the association with SGA outcome compared with cross-sectional third-trimester evaluation alone, improvements were clinically irrelevant (R^2 increase < 10%) for both SGA and late FGR.

Regarding prediction of SGA, the areas under the ROC curve (AUC) for 32-week AC z-score, AC z-velocity and conditional AC were 0.813 (95% CI, 0.787–0.838), 0.626 (95% CI, 0.593–0.659) and 0.560 (95% CI, 0.525–0.596), respectively (Figure 1). AUCs for AC *z*-velocity ($P < 0.001$) and conditional AC ($P < 0.001$) were significantly lower than the AUC of cross-sectional AC *z*-scores. When comparing longitudinal assessments, AC *z*-velocity performed significantly better than conditional AC ($P < 0.001$).

With regard to the prediction of late FGR, the AUC for 32-week AC *z*-score, AC *z*-velocity and conditional AC were 0.932 (95% CI, 0.903–0.961), 0.752 (95% CI, 0.712–0.792) and 0.655 (95% CI, 0.606–0.705), respectively (Figure 2). AUCs for AC *z*-velocity ($P < 0.001$) and conditional AC ($P < 0.001$) were significantly lower than the AUC of cross-sectional AC *z*-scores. When comparing longitudinal assessments, AC *z*-velocity performed significantly better than conditional AC ($P < 0.001$).

In terms of the detection rate of each approach for the diagnosis of SGA and late FGR, cross-sectional assessment (AC *z*-score) had better sensitivity than did the longitudinal approaches, irrespective of the fixed false-positive rate selected (Table 3).

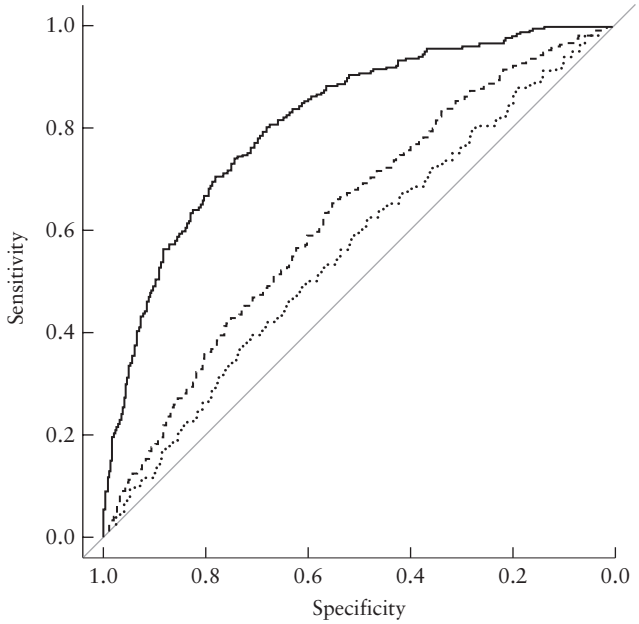

Figure 1 Receiver–operating characteristics curve of abdominal circumference (AC) *z*-score (——), AC *z*-velocity (- - - -) and conditional AC (·····) for prediction of small-for-gestational age (SGA; $n = 210$) in a cohort of 2696 singleton pregnancies. AC *z*-score measurements taken at 32 weeks' gestation and AC *z*-velocity and conditional AC measurements at 21 and 32 weeks' gestation.

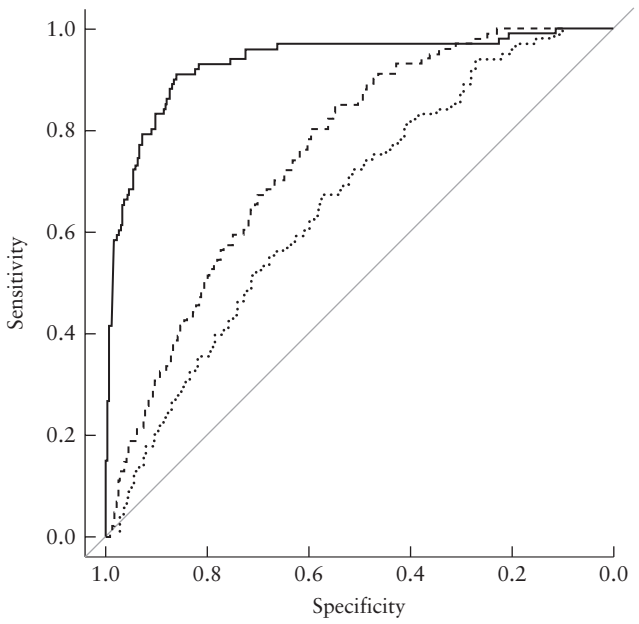

Figure 2 Receiver–operating characteristics curve of abdominal circumference (AC) *z*-score (——), AC *z*-velocity (- - - -) and conditional AC (·····) for prediction of late fetal growth restriction (FGR; $n = 103$) in a cohort of 2696 singleton pregnancies. AC *z*-score measurements taken at 32 weeks' gestation and AC *z*-velocity and conditional AC measurements at 21 and 32 weeks' gestation.

Table 3 Detection rate, at fixed false-positive rates (FPRs) of 5%, 10% and 15%, of small-for-gestational age (SGA; $n = 210$) and late fetal growth restriction (FGR; $n = 103$) in a cohort of 2696 singleton pregnancies, by assessment of abdominal circumference (AC) *z*-score, AC *z*-velocity or conditional AC

		Detection rate (95% CI) (%)		
Outcome	*Parameter*	*5% FPR*	*10% FPR*	*15% FPR*
SGA	AC *z*-score	32.3 (27–36.8)	49.2 (44.0–52.8)	59.0 (54.5–63.9)
	AC *z*-velocity	10.7 (7.9–14.9)	17.2 (12.9–21.6)	26.9 (21.5–31.3)
	Conditional AC	7.6 (4.5–10.4)	12.2 (9.3–16.7)	20.1 (15.6–24)
Late FGR	AC *z*-score	67.3 (61.4–76.3)	81.2 (75.3–88.1)	90.1 (87.1–96)
	AC *z*-velocity	18.8 (10.8–23.8)	28.7 (20.7–36.6)	39.6 (31.6–48.5)
	Conditional AC	9.9 (4.9–15.8)	19.8 (12.9–27.8)	29.7 (21.8–36.7)

AC *z*-score measurements were taken at 32 weeks' gestation. AC *z*-velocity and conditional AC measurements were taken at 21 and 32 weeks' gestation.

DISCUSSION

Despite many advances in prenatal diagnosis, detection of late FGR remains poor[14]. A longitudinal approach has been proposed as being more appropriate than cross-sectional evaluation, because the progressive nature of the condition is likely to be more amenable to detection by serial assessment[28]. Indeed, a recent survey[29] of 45 experts found approximately 75% agreement that slow growth should be a contributory criterion to define late FGR. Although this is conceptually sound, there is no evidence supporting this contention in low-risk pregnancy. Moreover, the optimal way to interpret the information obtained from serial measurements of a fetus is unclear. Our study revealed that longitudinal assessment of fetal growth from the second to third trimester by means of AC growth velocity[10,30] or conditional AC centiles[15] has a low predictive capacity for SGA and late FGR in low-risk pregnancy.

Our results are consistent with those of previous reports on longitudinal growth assessment, in which the use of conditional centiles did not add to cross-sectional evaluation. Hutcheon *et al.*[31] compared the association between abnormal perinatal outcome and cross-sectional 32-week EFWs with conditional growth from 32 weeks to birth in 9239 unselected pregnancies. They concluded that conditional growth assessment provided no improvement in the identification of adverse outcome. It is acknowledged by the authors that their window of growth assessment may not cover the critical period for growth restriction. However, our results suggest that there is no gain in longitudinally evaluating growth from the second to third trimester. Similarly, Sovio *et al.*[10] failed to find a significant association between second- to third-trimester slow AC growth velocity (in the lower centile) and adverse outcome (relative risk, 1.36; 95% CI, 0.97–1.9) in a large cohort of 3977 unselected nulliparous women. This association was even lower when only babies born with a normal birth weight were considered (relative risk, 0.61; 95% CI, 0.32–1.18).

Our study was not aimed at evaluating the performance of growth velocity in high-risk pregnancy. Several studies have addressed this issue[7,10,15,30,32] and consistently reported an association between slow growth velocity and adverse outcome. However, the diagnostic performance, in terms of specificity and sensitivity for adverse outcome, has not been evaluated.

When comparing longitudinal approaches for prediction of SGA or late FGR, AC *z*-velocity performed significantly better than did conditional AC. The reasons for this are beyond the scope of this study, but it can be hypothesized that conditional fetal growth centiles may need modification in order to be able to incorporate more than one previous weight measurement to reflect the optimal growth trajectory, allowing detection of pathological deviations[33]. Furthermore, the use of growth velocity is more intuitive and easier to use in clinical practice, irrespective of the availability of web-supported tools for conditional centile estimation[34].

Although it may seem intuitive that longitudinal assessment would be more suitable for capturing the dynamic nature of growth problems, it could be speculated that what really determines performance in predicting SGA and FGR is the ability to predict the size of the fetus at term[35,36]. In that sense, longitudinal assessment (in low-risk pregnancy) may only add false positives to size assessment[10,35]. It could be argued that this is because SGA and, to a lesser extent, FGR are defined by size, constituting a self-fulfilled prediction. The latter is consistent with our finding that, despite having a low predictive capacity, performance of longitudinal assessment was better in late FGR. We agree with the statement in a recent commentary[37] that the gold-standard definition of FGR should incorporate other functional parameters such as fetal Doppler, placental histology or biochemical evidence of an antiangiogenic situation or other neonatal/infant measurements. Indeed, in infants it has consistently been shown that growth velocity in early infancy is a better predictor of subsequent weight than is any cross-sectional measurement[38].

We acknowledge some limitations of our study. First, measurements at only two gestational ages (21 ± 2 and 32 ± 2 weeks) were considered; incorporating an additional (or alternative to the 32-week scan) measurement performed near term could improve detection, as has been reported in cross-sectional evaluation[10,39]. Only AC was considered in our study, as EFW is not validated in pregnancies below 24 weeks. It could be argued that excluding cases with abnormal growth assessment at 32 weeks constitutes a limitation. However, the rationale for such exclusion was that we wanted to detect incident cases, as opposed to prevalent cases, of late FGR. Also, because the conditional standards we used[26] were externally derived, it could be argued that baseline differences from the population on which the model was constructed (Scandinavian) resulted in an underperformance in our population. Finally, we note that, due to our definition of late FGR, some cases without prenatal Doppler evaluation may have been underdiagnosed.

In summary, longitudinal assessment of fetal growth by means of growth velocity or conditional centiles from the second to third trimester has a low predictive capacity for SGA and late FGR in low-risk pregnancy.

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