

Single-Time-Point Fetal Mitral E/A Ratio as A Predictor of Neonatal Intensive Care Unit Admission in Late-Onset Fetal Growth Restriction

Geç Başlangıçlı Fetal Büyüme Kısıtlılığında Yenidoğan Yoğun Bakım Ünitesi Yatışının Öngörücüsü Olarak Tek Zamanlı Fetal Mitral E/A Oranı

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ABSTRACT

Aim: Aim: To investigate whether the fetal mitral E/A ratio, a Doppler index of left ventricular diastolic function, is associated with neonatal intensive care unit (NICU) admission in late-onset fetal growth restriction (FGR).

Materials and Methods: In this retrospective single-center study, 41 fetuses with late-onset FGR (diagnosed after 32 weeks by Delphi consensus criteria) with complete data were analyzed. The fetal mitral E/A ratio was measured by pulsed-wave Doppler at diagnosis, independent of clinical management. The primary outcome was NICU admission. Groups were compared with the Mann–Whitney U and Fisher exact tests, and discrimination was assessed by receiver-operating-characteristic (ROC) analysis with Youden-derived cut-offs.

Results: Ten neonates (24.4%) were admitted to the NICU. The fetal mitral E/A ratio was significantly higher in admitted than in non-admitted neonates (0.84 vs 0.63; $p=0.021$), driven mainly by a lower A-wave velocity. The E/A ratio predicted NICU admission with an area under the curve of 0.75; a cut-off above 0.79 yielded 70% sensitivity and 94% specificity. A lower cerebroplacental ratio ($p=0.006$), middle cerebral artery pulsatility index ($p=0.011$), estimated fetal weight percentile ($p=0.017$), and birth weight ($p=0.023$) were also associated with admission.

Conclusion: In late-onset FGR, a higher fetal mitral E/A ratio was associated with NICU admission and predicted it with high specificity. This simple, reproducible index may complement existing surveillance parameters, pending validation in larger prospective cohorts.

Keywords: Fetal growth restriction; Fetal Echocardiography; Mitral E wave, Mitral A wave, Intensive care units; neonatal; prenatal

ÖZ

Amaç: Sol ventrikül diastolik fonksiyonunun bir Doppler indeksi olan fetal mitral E/A oranının, geç başlangıçlı fetal büyüme kısıtlılığında (FBK) yenidoğan yoğun bakım ünitesi (YYBÜ) yatışı ile ilişkisini araştırmak.

Gereç ve Yöntemler: Bu retrospektif tek merkezli çalışmada, Delphi uzlaşi kriterlerine göre 32. gebelik haftasından sonra tanı alan, verileri tam geç başlangıçlı FBK'li 41 fetüs analiz edildi. Fetal mitral E/A oranı tanı anında, klinik yönetimden bağımsız olarak pulsed-wave Doppler ile ölçüldü. Birincil sonlanım YYBÜ yatışıydı. Gruplar Mann–Whitney U ve Fisher kesin testleriyle karşılaştırıldı; ayırt edicilik, Youden indeksiyle belirlenen eşik değerler kullanılarak ROC analiziyle değerlendirildi.

Bulgular: On yenidoğan (%24,4) YYBÜ'ye yatırıldı. Fetal mitral E/A oranı, yatırılan yenidoğanlarda yatırılmayanlara göre anlamlı olarak daha yüksekti (0,84'e karşı 0,63; $p=0,021$) ve bu fark esas olarak düşük A-dalga hızından kaynaklanıyordu. E/A oranı YYBÜ yatışını 0,75 eğri altı alanla öngördü; 0,79 üzerindeki eşik değeri %70 duyarlılık ve %94 özgüllük sağladı. Düşük serebroplasental oran ($p=0,006$), orta serebral arter pulsatilite indeksi ($p=0,011$), tahmini fetal ağırlık persentili ($p=0,017$) ve doğum ağırlığı ($p=0,023$) da yatışla ilişkililiydi.

Sonuç: Geç başlangıçlı FBK'de yüksek fetal mitral E/A oranı YYBÜ yatışıyla ilişkililiydi ve bunu yüksek özgüllükle öngördü. Bu basit ve tekrarlanabilir indeks, daha büyük prospektif kohortlarda doğrulanması koşuluyla mevcut izlem parametrelerini tamamlayabilir.

Anahtar Kelimeler: Fetal büyüme kısıtlılığı; Fetal ekokardiyografi; Mitral E dalgası; Mitral A dalgası; Yoğun bakım ünitesi; Neonatal; Prenatal

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INTRODUCTION

Fetal growth restriction (FGR) represents the failure of a fetus to attain its biologically determined growth potential and remains a major challenge in perinatal medicine (1). Arising predominantly from an unfavorable intrauterine environment, it accounts for a disproportionate share of perinatal mortality and is implicated in adverse outcomes that extend beyond the neonatal period, placing risk stratification and prognostic assessment of affected fetuses at the forefront of perinatal research (2).

The most common underlying mechanism of FGR is uteroplacental insufficiency, in which impaired placental development and perfusion restrict oxygen and nutrient delivery to the fetus. The resulting rise in placental vascular resistance increases ventricular afterload, while chronic hypoxemia and undernutrition promote myocardial remodeling and impaired contractility (3-4). These changes disturb both loading conditions and intrinsic myocardial performance, ultimately reducing cardiac output. Reduced cardiac output is thus both a consequence of the disease process and a driver of further fetal compromise, contributing to the circulatory redistribution ("brain-sparing") that characterizes progressive FGR (5). Diastolic function is particularly vulnerable, as impaired ventricular relaxation and reduced compliance alter ventricular filling, a change that can be captured non-invasively through the atrioventricular inflow pattern (6).

As a result of this chronic intrauterine adaptation, growth-restricted fetuses are strong candidates for postnatal morbidity, including respiratory, metabolic, and neurological complications that frequently require neonatal intensive care unit (NICU) admission (7). Anticipating this postnatal course antenatally would support delivery planning, neonatal resource allocation, and parental counseling. Among the echocardiographic indices that may aid such prediction, the mitral E/A ratio is especially appealing because it is simple, rapidly obtainable, and reproducible, and it directly reflects left ventricular diastolic function (8). In the present study, we therefore investigated whether the fetal mitral E/A ratio is associated with NICU admission in neonates with late-onset FGR.

MATERIALS AND METHODS

Study design and setting. This was a retrospective, single-center study conducted at a tertiary training and research hospital between June 2025 and July 2026. Data were retrieved from the electronic records of pregnancies evaluated for fetal growth restriction during the study period. These pregnancies were managed across separate departments: fetal echocardiography by

the pediatric cardiologist, and antenatal surveillance and obstetric management independently by the perinatology and obstetrics teams; postnatal care was provided by the neonatology service. The study was approved by the institutional ethics committee (approval no.:689231) and conducted in accordance with the Declaration of Helsinki; given the retrospective design, the requirement for written informed consent was waived.

Study population and definition of late-onset FGR. Only fetuses with late-onset fetal growth restriction (FGR), defined as a diagnosis established at a gestational age of more than 32 weeks (9), were eligible. The diagnosis was based on the Delphi consensus criteria for late FGR (10-11): an estimated fetal weight (EFW) or abdominal circumference (AC) below the 3rd centile as a solitary criterion, or an EFW/AC below the 10th centile in combination with at least two of the following — a cerebroplacental ratio below the 5th centile, an umbilical artery pulsatility index above the 95th centile, or a fall in AC or EFW crossing more than two quartiles on growth centiles. Gestational age was confirmed by first-trimester crown-rump length. Fetuses with major structural malformations, congenital heart disease, confirmed or suspected chromosomal or genetic abnormalities, congenital infection, or multiple gestation were excluded, as were constitutionally small fetuses not meeting the above criteria and cases with inadequate Doppler acquisition.

Fetal echocardiography and Doppler measurements. Fetal echocardiography was performed by a single pediatric cardiologist at the time of diagnosis using, and the mitral E/A ratio was obtained routinely. Left ventricular diastolic function was assessed from the mitral inflow pattern (6,12). Peak early (E) and late atrial (A) diastolic velocities were measured by pulsed-wave Doppler with the sample volume positioned at the tips of the mitral valve leaflets in the apical four-chamber view, with the insonation beam aligned as parallel as possible to the direction of inflow. When a parallel angle could not be obtained from the four-chamber view because of fetal position, the transducer was angled to acquire a sagittal/oblique plane displaying the left ventricular outflow tract (LVOT), from which the mitral valve was interrogated to improve beam-to-flow alignment (Figure 1). If near-parallel alignment (insonation angle below 20°) still could not be achieved, the case was excluded. Measurements were obtained during fetal quiescence and averaged over ≥ 3 consecutive cardiac cycles, and the E/A ratio was calculated. The E/A ratio obtained at this single time point was used for analysis.

Clinical management and timing of delivery. The mitral E and A waves were obtained solely for this study and were not used in clinical decision-making. Antenatal surveillance — including the cerebroplacental ratio (CPR), umbilical artery and middle cerebral

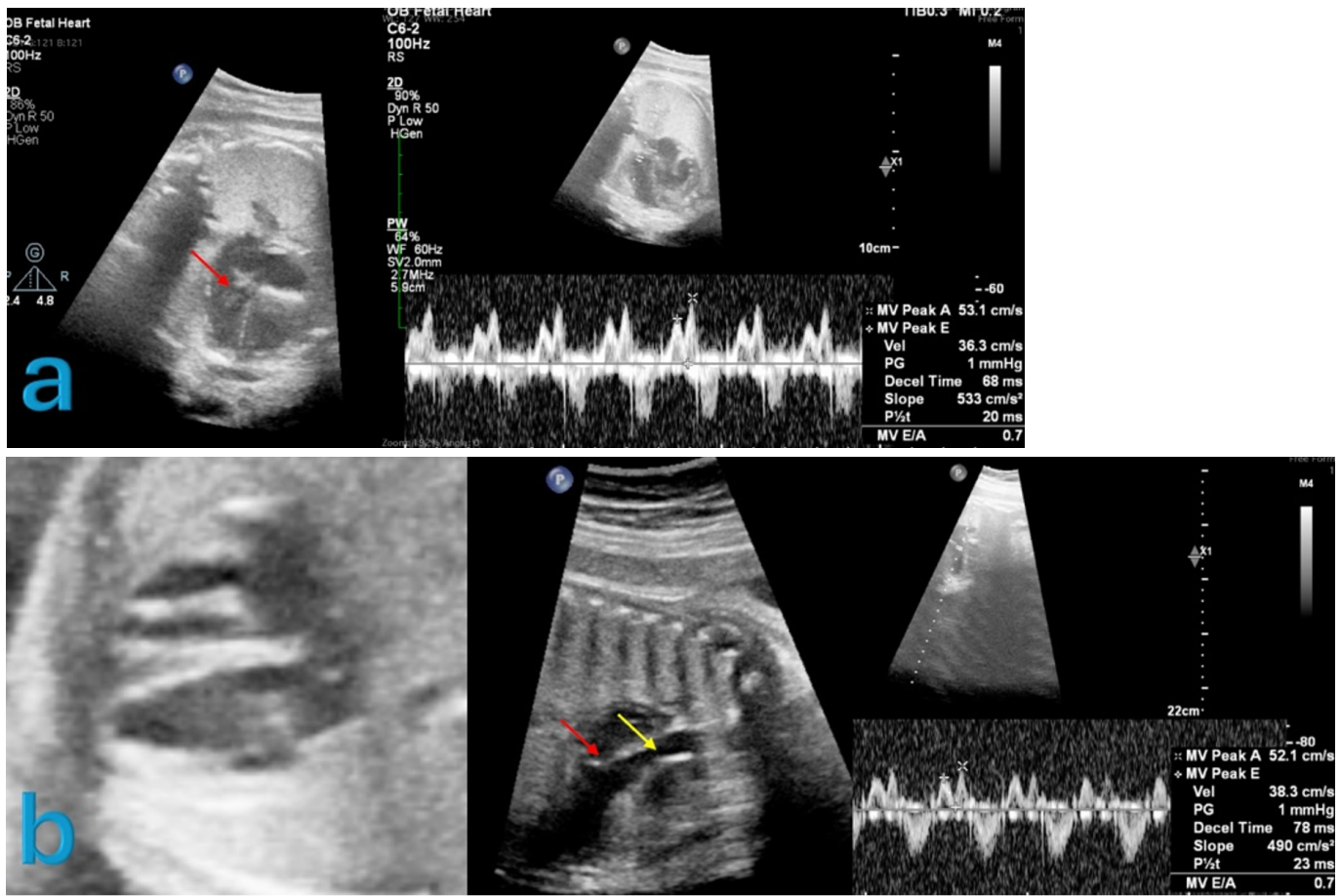


Figure 1. Acquisition of the fetal mitral E and A waves by pulsed-wave Doppler. (a) In the apical four-chamber view, with the insonation beam aligned parallel to the direction of mitral inflow (red arrow), the pulsed-wave Doppler sample volume is positioned at the tips of the mitral valve leaflets to record the early passive (E) and late atrial (A) diastolic filling velocities, from which the mitral E/A ratio is calculated. (b) When a parallel angle cannot be obtained in the four-chamber view because of fetal position, the transducer is turned to a near-vertical, sagittal/oblique plane that displays the left ventricular outflow tract (yellow arrow) – a projection comparable to that used to image the aortic arch – thereby restoring near-parallel beam-to-flow alignment with the mitral valve (red arrow) and allowing a rapid pulsed-wave Doppler measurement of the mitral E and A velocities. E, peak early (passive) diastolic velocity; A, peak late (atrial) diastolic velocity.

artery Doppler, biophysical profile, and amniotic fluid assessment — was performed by the perinatology and obstetrics teams, who also determined the timing and mode of delivery (13). These decisions were made independently of the fetal diastolic function findings.

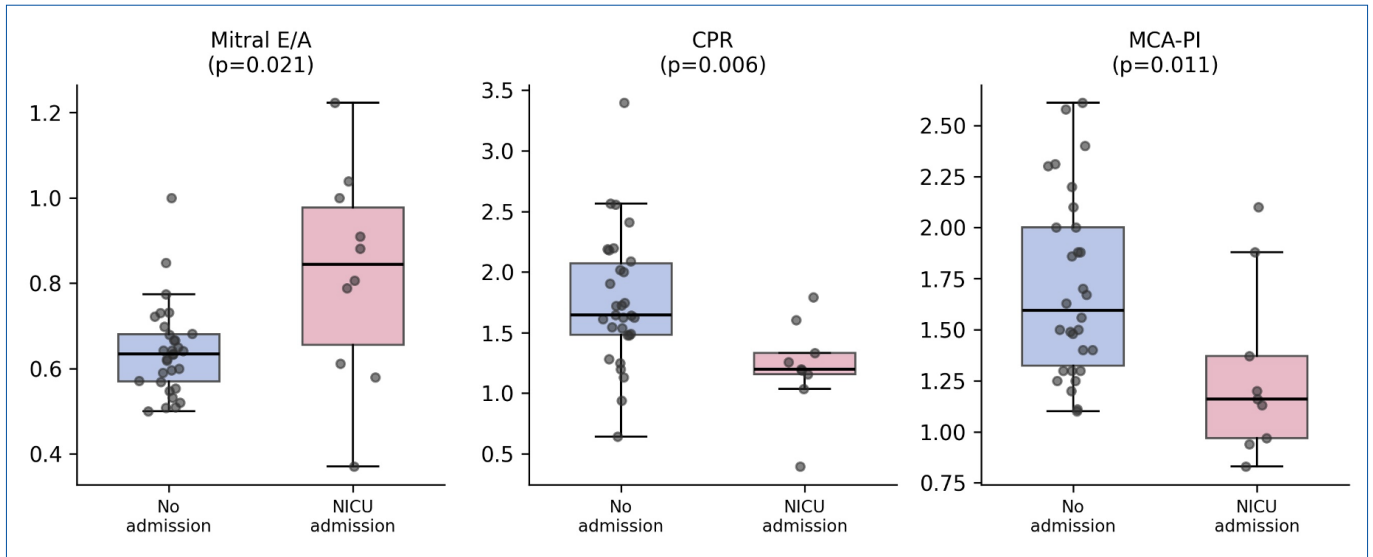
Neonatal outcomes. After birth, the decision for NICU admission and subsequent follow-up was made by the attending neonatologist and pediatrician, independent of the fetal echocardiographic findings. The primary outcome was admission to the NICU. Reasons for admission were classified as respiratory (respiratory distress syndrome, transient tachypnea, or need for respiratory support), metabolic (hypoglycemia), infectious (suspected or proven sepsis), hyperbilirubinemia requiring phototherapy, and other prematurity-related care. NICU length of stay was summarized descriptively among admitted neonates.

Statistical analysis. Continuous variables were expressed as median with interquartile range (IQR) and categorical variables as counts. The normality of distributions was assessed with the Shapiro–Wilk test. The fetal mitral E/A ratio and the secondary Doppler and biometric parameters were compared between neonates who were and were not admitted to the NICU using the Mann–Whitney U test, with the rank-biserial correlation reported as an effect size; categorical variables were compared using the Fisher exact test. Predictive ability was assessed by receiver-operating-characteristic (ROC) analysis; the area under the curve (AUC) was reported with a 95% confidence interval, and the optimal cut-off identified by the Youden index with corresponding sensitivity, specificity, and predictive values. Given the limited number of events, these analyses were exploratory. A two-sided p value below 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 32 (IBM Corp., Armonk, NY, USA).

Table 1. Comparison of maternal, fetal Doppler, biometric, and neonatal variables between neonates with and without NICU admission.

Variable	NICU admission (n=10)	No admission (n=31)	p
Maternal age (years)	30.50 [24.00–35.50]	25.00 [22.00–28.00]	0.182
GA at assessment (weeks)	35.36 [32.61–35.93]	35.21 [34.25–36.86]	0.425
EFW percentile	5.90 [2.30–9.80]	13.50 [7.83–22.45]	0.017
Mitral E/A ratio	0.84 [0.66–0.98]	0.63 [0.57–0.68]	0.021
MCA-PI	1.16 [0.97–1.37]	1.59 [1.32–2.00]	0.011
UA-PI	1.05 [0.87–1.09]	0.97 [0.86–1.10]	0.505
CPR	1.20 [1.15–1.33]	1.64 [1.48–2.07]	0.006
Birth weight (g)	2360.00 [1965.00–2595.00]	2600.00 [2375.00–2900.00]	0.023
GA at birth (weeks)	37.00 [36.78–37.31]	37.42 [37.00–39.34]	0.108
Birth weight percentile	7.55 [6.33–12.90]	15.30 [7.00–42.20]	0.136

GA, gestational age; EFW, estimated fetal weight; MCA-PI, middle cerebral artery pulsatility index; UA-PI, umbilical artery pulsatility index; CPR, cerebroplacental ratio; IQR, interquartile range. Values are median [IQR]; p values from the Mann-Whitney U test.

**Figure 2.** Distribution of the fetal mitral E/A ratio, CPR, and MCA-PI in neonates with and without NICU admission. Boxes show the median and IQR; points are individual cases; p values from the Mann-Whitney U test.

RESULTS

Study population. Forty-three fetuses with late-onset FGR were evaluated, of whom 41 had complete data for the fetal mitral E/A ratio and neonatal outcome and formed the analysis cohort. The median gestational age at echocardiographic assessment was 35.5 weeks (IQR 34.1–36.6; range 32.0–38.8). The median maternal age was 26 years (IQR 21.8–31.3), with a median gravida of 2 and para of 1. An accompanying pathology was recorded in a minority of cases (symmetric FGR in 5 fetuses and a right aortic arch in 1). Delivery was vaginal in 29 (70.7%) and by cesarean section in 12 (29.3%); 22 neonates were male and 19 female.

Fetal biometry. The median estimated fetal weight was 2139 g (IQR 1840–2318), corresponding to an EFW percentile of 11.8 (IQR 5.9–22.5) by the INTERGROWTH-21st standard (14). The individual biometric percentiles showed the asymmetric pattern typical of FGR, with the abdominal circumference most severely affected (AC percentile 2.6 [IQR 0.8–6.8]) and relative preservation of the head and femur measurements.

Fetal Doppler parameters. Across the cohort, the median mitral E velocity was 30.0 cm/s (IQR 26.0–35.5) and the mitral A velocity 49.5 cm/s (IQR 41.3–53.0), giving a mitral E/A ratio of 0.64 (IQR 0.58–0.76). The median MCA-PI was 1.50 (IQR 1.25–2.00), the UA-PI 0.99 (IQR 0.86–1.10), and the CPR 1.60 (IQR 1.25–1.91).

Table 2. Diagnostic performance of fetal parameters for the prediction of NICU admission.

Parameter	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Mitral E/A	0.75 (0.48–0.96)	> 0.79	70	94	78	91
CPR	0.81 (0.64–0.94)	< 1.33	78	80	54	92
MCA-PI	0.79 (0.55–0.97)	< 1.20	67	90	67	90
EFW percentile	0.77 (0.57–0.93)	< 11.40	89	67	44	95

AUC, area under the curve; CI, confidence interval; CPR, cerebroplacental ratio; MCA-PI, middle cerebral artery pulsatility index; EFW, estimated fetal weight; PPV, positive predictive value; NPV, negative predictive value. Cut-offs were identified by the Youden index.

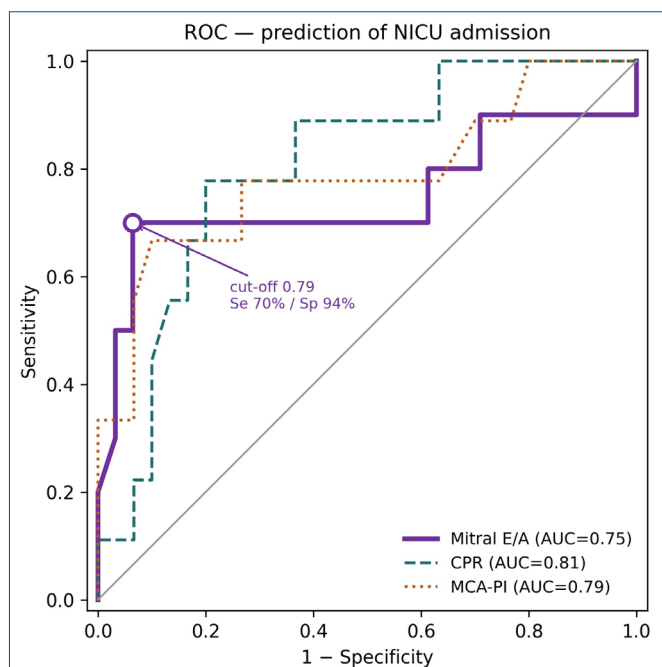


Figure 3. Receiver-operating-characteristic curves for the fetal mitral E/A ratio (primary), CPR, and MCA-PI in predicting NICU admission. The circle marks the optimal E/A cut-off (0.79) by the Youden index.

Mitral E/A ratio and NICU admission. Ten of the 41 analyzed neonates (24.4%) were admitted to the NICU. The fetal mitral E/A ratio was significantly higher in admitted than in non-admitted neonates (median 0.84 [IQR 0.66–0.98] vs 0.63 [0.57–0.68]; Mann–Whitney $U = 231.5$, $p = 0.021$; rank-biserial $r \approx 0.49$; Table 1, Figure 2). This difference was driven mainly by a lower A-wave velocity in the admitted group (median 37.5 vs 50.0 cm/s; $p = 0.107$), whereas the E-wave velocity was similar between groups ($p = 0.939$). On ROC analysis, the E/A ratio predicted NICU admission with an AUC of 0.75 (95% CI 0.48–0.96); an optimal cut-off of 0.79 by the Youden index yielded a sensitivity of 70% and a specificity of 94% (Figure 3, Table 2).

Secondary associations with NICU admission. Several parameters differed significantly between admitted and non-admitted neonates: a lower CPR (1.20 vs 1.64; $p = 0.006$), a lower MCA-PI (1.16 vs

1.59; $p = 0.011$), a lower EFW percentile (5.9 vs 13.5; $p = 0.017$), a lower birth weight (2360 vs 2600 g; $p = 0.023$), and lower Apgar scores at 1 minute ($p = 0.014$) and 5 minutes ($p < 0.001$). The umbilical artery pulsatility index did not differ between groups, consistent with the frequently preserved umbilical flow in late-onset FGR, and the gestational age at assessment, gestational age at birth ($p = 0.108$), birth weight percentile ($p = 0.136$), maternal age, gravida, and para showed no significant differences. On ROC analysis, the CPR and MCA-PI achieved the highest discrimination for NICU admission (AUC 0.81 and 0.79, respectively; Table 2).

Neonatal outcomes. Among the 10 admitted neonates, the median length of NICU stay was 4 days (IQR 3.2–7.2; range 1–24). Respiratory support was required in the majority (continuous positive airway pressure in 5 and mechanical ventilation in 1). The recorded morbidities comprised transient tachypnea of the newborn in 4, respiratory distress syndrome in 3, hypoglycemia in 5, sepsis in 2, and hyperbilirubinemia requiring phototherapy in 1.

DISCUSSION

FGR most often results from placental insufficiency and is among the most common complications of pregnancy, affecting approximately 5–10% of newborns (1). Its clinical importance is disproportionate to its frequency: often unrecognized antenatally, FGR underlies roughly one-half of stillbirths (about 52%) and approximately 10% of perinatal deaths, is the single largest contributor to perinatal mortality among non-anomalous fetuses, and carries an approximately eight-fold increase in stillbirth risk (15). Even when stillbirth is averted, affected neonates face a substantially higher burden of morbidity — including respiratory distress syndrome, birth asphyxia, hypoglycemia, polycythemia, hyperbilirubinemia, necrotizing enterocolitis, and late-onset sepsis — with a frequent need for NICU admission (2). The consequences extend well beyond the neonatal period, as FGR induces cardiac remodeling and metabolic programming that persist into childhood and confer an increased risk of cardiovascular and metabolic disease in adult life (16–17). Late-onset FGR (≥ 32 weeks), which constituted our

cohort and represents the majority of cases, is often regarded as more benign than early-onset disease but nonetheless carries appreciable risks of late preterm birth, sudden fetal deterioration, and adverse neonatal outcome (9,18).

The transmitral E/A ratio is a Doppler index of left ventricular diastolic function expressing the balance between early passive filling (E wave) and late atrial filling (A wave) (19). Because the immature fetal myocardium is relatively non-compliant and depends heavily on atrial contraction, fetal filling is normally A-dominant, yielding an E/A ratio below unity that rises gradually toward term as ventricular relaxation and compliance improve (8). In the setting of placental insufficiency, chronically increased afterload and hypoxia-mediated myocardial remodeling impair diastolic function, and altered ventricular relaxation and loading shift this filling balance, producing an abnormal E/A ratio (19-20). In our cohort, the fetal mitral E/A ratio was significantly higher in neonates who subsequently required NICU admission than in those who did not (0.84 vs 0.63), driven principally by a lower A-wave velocity. This direction is concordant with reports of an increased transmitral E/A ratio in growth-restricted infants (for example, 0.84 vs 0.78 in preterm FGR), in whom diastolic indices correlated with the duration of respiratory support (21), supporting a link between fetal diastolic dysfunction and postnatal morbidity. However, the literature is not uniform: some studies and a recent meta-analysis found no significant difference in the mitral E/A ratio between growth-restricted and appropriately grown fetuses (22), likely reflecting differences in FGR severity, gestational age, and measurement technique. Our findings suggest that, at least in late-onset FGR, a higher E/A ratio identifies fetuses at greater risk of an adverse neonatal course.

A practical strength of the mitral E/A ratio is its accessibility. Unlike advanced modalities such as tissue Doppler imaging, the myocardial performance (Tei) index, or two-dimensional speckle-tracking and fetal heart quantification, which require specialized software, offline analysis, or particular expertise (20,23), the E/A ratio is obtained from a single pulsed-wave Doppler tracing of mitral inflow and can be measured rapidly during routine fetal echocardiography. It can therefore be incorporated into routine surveillance of growth-restricted fetuses without additional equipment or scanning time and reproduced by any operator performing fetal echocardiography.

To our knowledge, this is the first study evaluating the fetal mitral E/A ratio as a predictor of NICU admission specifically in late-onset FGR. Notably, in our cohort the E/A ratio predicted NICU admission and showed promising discriminatory ability. An elevated fetal E/A ratio therefore appears relatively specific for neonates requiring intensive care, so that a high value could flag pregnancies

warranting intensified surveillance, delivery in an appropriately resourced setting, and neonatal team readiness. The lower sensitivity indicates that a normal E/A ratio does not exclude risk and should not, in isolation, reassure; the index is best regarded as a specific “rule-in” marker.

Limitations. This study has several limitations. It was a retrospective, single-center analysis of a modest sample with few NICU admissions; the analyses, particularly the ROC-derived cut-off, should be regarded as exploratory, and the confidence interval around the AUC was correspondingly wide. The mitral E/A ratio was obtained at a single time point at diagnosis, precluding assessment of its longitudinal trajectory. The individual fetal biometric percentiles were derived from the recorded biometric age rather than from raw measurements and are therefore approximate. Finally, NICU admission is a composite, partly subjective outcome influenced by local practice, and residual confounding — for example, by gestational age — cannot be excluded. Also due to the limited number of NICU admissions (n=10), multivariable logistic regression could not be performed without substantial risk of overfitting. Therefore, the independent predictive value of the mitral E/A ratio beyond established Doppler indices remains to be confirmed. Larger, prospective, multicenter studies are needed to validate the proposed cut-off and to define the incremental value of the E/A ratio over established Doppler indices (24-25).

CONCLUSION

In fetuses with late-onset FGR, a higher fetal mitral E/A ratio was associated with subsequent NICU admission and predicted it with high specificity. As a simple, rapidly obtainable, and reproducible index of left ventricular diastolic function, the mitral E/A ratio may complement existing surveillance parameters in identifying growth-restricted fetuses at increased risk of adverse neonatal outcome, pending validation in larger prospective cohorts.

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