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DOI:
10.1111/aogs.13123

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Received Date : 04-Oct-2016
Revised Date : 06-Feb-2017
Accepted Date : 08-Feb-2017
Article type : Original Research Article

Is the first urinary albumin/creatinine ratio (ACR) in women with suspected pre-eclampsia a prognostic factor for maternal and neonatal adverse outcome? A retrospective cohort study

Running Headline: Urinary ACR and adverse outcomes

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Conflicts of Interest: The authors have no conflicts of interest

Abstract

Introduction: The aim of this study was to determine the prognostic value of the first urinary albumin/creatinine ratio (ACR) for adverse maternal and neonatal outcomes and how it relates to other prognostic factors. *Material and methods:* We performed a retrospective cohort study from December 2009 to February 2012 with analysis of demographic, clinical and biochemical data from two obstetric day assessment units in hospitals in Southeast Scotland. We included 717 pregnant women, with singleton pregnancies after 20 weeks gestation, referred for evaluation of suspected pre-eclampsia and having their first ACR performed. The ability of ACR to predict future outcomes was assessed in both univariable and multivariable logistic regression models. The latter assessed its prognostic value independent to (adjusting for) existing prognostic factors. Primary outcome measures were maternal and neonatal composite adverse outcomes, and a secondary outcome was gestation at delivery. *Results:* 204 women (28.5%) experienced a composite adverse maternal outcome. 146 women (20.4%) experienced a composite adverse neonatal outcome. Multivariate analysis of log-transformed ACR, demonstrated that a 1-unit increase in log ACR is associated with an increased odds of adverse maternal (Odds Ratio 1.60, 95% CI 1.45-1.80) and adverse neonatal (Odds Ratio 1.15, 95% CI 1.02-1.29) composite outcomes, and with reduced gestational age at delivery (coefficient: -0.46, 95% CI -0.54 to -0.38). *Conclusions:* ACR is an independent prognostic factor for maternal and neonatal adverse outcomes in suspected pre-eclampsia. ACR may be useful to inform risk predictions within a prognostic model.

Keywords:
pre-eclampsia, cohort study, ACR, albumin to creatinine ratio, risk factors, prognosis, adverse events

Abbreviations

ACR	albumin to creatinine ratio
BMI	body mass index
BP	blood pressure
OR	odds ratio
RR	risk ratio
MAP	mean arterial blood pressure

Key Message

Albumin to creatinine ratio is an independent prognostic factor for maternal and neonatal adverse outcomes in suspected pre-eclampsia though the prognostic value appears larger for maternal outcomes. Therefore albumin to creatinine ratio could play an important role in healthcare research and clinical practice in the future.

Introduction

Pre-eclampsia is defined as the presence of raised blood pressure (BP; ≥140/90mmHg) after 20 weeks gestation, in a previously normotensive non-proteinuric patient with one or more of the following; significant proteinuria (≥ 0.3g/24hours), maternal organ dysfunction or uteroplacental dysfunction (1,2). Suspected pre-eclampsia is the most frequent clinical presentation to obstetric units. Pre-eclampsia is associated with severe complications such as seizures, stroke, multiple organ failure and perinatal mortality, if not recognised and managed properly.

The spot urinary protein to creatinine ratio and the albumin to creatinine ratio (ACR) have been studied in patients with renal disease, diabetes and pre-eclampsia to assess proteinuria. Albumin excretion is considered to reflect glomerular damage more accurately than total protein excretion, and albuminuria may be a marker of systemic endothelial cell dysfunction (3). The majority of international organisations now recommend spot proteinuria tests in the assessment of suspected pre-eclampsia. ACR has been shown to be an accurate indicator of proteinuria in women with pre-eclampsia (4-6). Despite this evidence the obstetric community has not widely adopted the use of ACR as yet and protein to creatinine ratio or 24-hour urine collection are more commonly employed.

As well as being useful in the diagnosis of pre-eclampsia (4,6), ACR has potential to be useful in predicting adverse pregnancy outcomes (7,8). New prognostic factors are needed in this area (9-12). Prognostic factors can guide clinical decision-making, patient counselling, and inform the design and analysis of new trials (10-12). They can also improve prognostic models, which produce absolute risk predictions for women based on a set of individual characteristics (9). Before including a new factor in a prognostic model, it is important to quantify its independent prognostic value over and above existing prognostic factors. Factors that add additional (independent) prognostic information are difficult to find, but are necessary to improve the discrimination performance of prognostic models (12).

The aim of this study was to examine the prognostic value of baseline ACR (ACR at first presentation) to predict maternal and neonatal adverse outcomes in women referred with suspected pre-eclampsia There were two objectives: (i) to examine if ACR is prognostic for adverse maternal and neonatal outcomes when no other factor is considered (unadjusted prognostic effect) and (ii) to evaluate whether ACR is a prognostic factor for such outcomes after adjusting for existing prognostic factors (independent prognostic effect).

Material and methods

Study Design

We performed a retrospective cohort study of pregnant women undergoing ACR test in the obstetric Day Assessment Units of two hospitals in National Health Service Lothian trust between December 2009 and February 2012. The Simpson Centre for Reproductive Health is a tertiary referral centre with more than 6,500 deliveries per annum. St John's Hospital is a district general hospital with approximately 2,600 deliveries per annum. Women were excluded if they had not delivered by the end of February 2012.

All pregnant women with urinary ACR results were identified from biochemistry database (APEX, ApexHealthware). Women were included if they had booked for their pregnancy prior to 14 weeks and if they were referred from primary care to the hospital Day Assessment Unit with suspected pre-eclampsia (suspected hypertension [generally ≥140/90mmHg] and at least 1+ proteinuria on dipstick testing). Women were excluded if they had multiple pregnancy, proteinuric renal disease, proven urinary tract infection or if the ACR was measured for another indication (for example diabetes). Women who had their first ACR sent

prior to 20 weeks of gestation were also excluded as this suggests a chronic hypertensive or proteinuric disorder or underlying renal pathology.

We performed systematic review of medical records collecting predefined characteristics (demographic and clinical) to maximize accuracy and minimise missing data. We used multiple data sources to collect neonatal outcome data, in order to increase confidence that no cases of perinatal mortality or significant morbidity were missed. Data were acquired from the maternity electronic patient records database TRAK (supplied by Intersystems) and the neonatal unit electronic patient records database BadgerNet (supplied by Clevermed) systems. Demographic features were recorded at booking visit, clinical and laboratory data at the time of first ACR measurement and subsequent antenatal visits and at delivery, and the outcome of mothers and babies were collected on every pregnancy.

ACR measurement taken on first hospital assessment for suspected pre-eclampsia was used in the analysis (i.e. follow up measurements were not included). ACR was calculated from urine samples in the biochemistry labs of The Royal Infirmary of Edinburgh. Immunoassays (Abbott Architect), turbidmetric and kinetic alkaline picrate (Jaffe) were used to calculate the concentrations of albumin and creatinine respectively in the urine sample. From this the albumin (mg/L)/urine creatinine (mmol/L) was calculated.

Existing prognostic factors were: gestational age at ACR measurement, essential hypertension, pre-existing diabetes, gestational diabetes, social deprivation index, body mass index (BMI), mean arterial BP, current smoking status, parity and maternal age recorded from the clinical record at booking (< 14 weeks). Deprivation was recorded as social multiple index of deprivation [a postcode based Scottish Index of multiple deprivation from 2012 - five groups ranging from most deprived index (1) to least deprived index (5)] (13). BMI was recorded as [< 18.5, 18.5 − 24.99, 25.0 − 29.99, 30.0 − 34.9, 35.0 − 39.9 and > 40] and mean arterial BP(MAP) [diastolic BP+ 1/3 (systolic BP-diastolic BP]. MAP was used in place of systolic or diastolic BP, because previous evidence suggests it is a better prognostic factor for pre-eclampsia compared to BP measured during the first or second trimester of pregnancy (14). Data on development of gestational diabetes (to allow exclusion and diagnosed using Scottish Intercollegiate Guidelines network guideline (15)) and gestation at ACR (days) were also recorded.

The primary maternal outcome was a composite adverse maternal outcome, defined as one or more of: use of intravenous magnesium sulphate for seizure prophylaxis, use of intravenous anti-hypertensives, admission to intensive care unit / or high dependency unit for hypertension, placental abruption, eclampsia or HELLP (Haemolysis, Elevated Liver enzymes, low platelets). The primary neonatal outcome was a composite adverse neonatal outcome, defined as one or more of: iatrogenic preterm delivery <34 weeks, birth weight <5th centile (calculated from sex-specific birth weight centile charts) (16), , abnormal umbilical artery Doppler [absent or reversed end-diastolic (ARED) flow], arterial cord pH<7.1, need for ventilation, neonatal or intrauterine death. Secondary outcome was gestation at delivery (weeks).

No formal power calculation was performed, and we included all data available over a three-year time period to maximise sample size. In prognosis research, a typical rule of thumb is that at least ten events (cases with the outcome of interest) are required to evaluate every one candidate prognostic variable (17). In our study over 200 women had a maternal composite adverse outcome, thus the sample size was considered adequate for the analysis performed.

3.9% of women had one or more missing values for data on existing prognostic factors. Due to the small proportion missing we considered a complete case multivariable analysis sufficient (18).. Thus, only a complete case analysis was performed, and the relatively few women with missing data were excluded for the multivariable analysis but included in the ACR only analysis.

Primary analyses

The baseline characteristics of the sample were summarised by primary outcome status with differences between groups assessed using unpaired t-tests or Mann Whitney U tests for continuous and χ^2-tests for binary data.

Univariable and multivariable logistic regression models were used to examine the unadjusted and the adjusted (independent) prognostic association of ACR with each binary primary outcome. The multivariable analysis adjusted for a pre-defined set of factors that we considered to be prognostic factors, as described above .

For the continuous variable "ACR" the assumption of linearity of the prognostic effect on the log-odds scale was examined using fractional polynomials. Fractional polynomials of degree two were used to obtain an appropriate transformation for ACR, for which the linearity assumption did not hold (19). This suggested that a logarithmic transformation was needed for ACR. Thus, the logistic models estimated the prognostic value of ACR as summarised by an (adjusted) odds ratio (OR), giving the (adjusted) relative odds of the outcome for two individuals that differ in log-ACR by 1-unit. To avoid deletion of patients with undefined log transformed ACR values (log (0)), 0.01 was added across all the entries of ACR following transformation of the data.

Similarly, univariable and multivariable models were fitted for the secondary outcome, gestation weeks at delivery using linear rather than logistic regression.

For the neonatal composite outcome gestational age at ACR measurement was adjusted for as a binary outcome after categorizing to age<34 weeks and age ≥ 34 weeks. This categorization was enforced by the clinical team in advance of the analysis as: 1) Women who had the first ACR test before 34 weeks represented a group with suspected pre-term pre-eclampsia versus women with suspected later onset pre-eclampsia, 2) Pre-term pre-eclampsia is a more severe clinical condition and more often associated with neonatal adverse outcome including premature delivery, and 3) Part of the composite adverse neonatal outcome is iatrogenic pre-term delivery prior to 34 weeks. The rationale was based on the existing literature (20-23).

Secondary analysis

The discrimination performance of the entire multivariable model was summarised to ascertain its potential as a prognostic model, using the apparent C statistic [area under the receiver operating characteristic (ROC) curve] where 0.5 indicates no discrimination (between those with and those without the outcome) beyond chance and 1 indicates perfect discrimination. The C-statistic is equivalently defined as the probability that the predicted risk for a randomly selected individual with the outcome is higher than that for a randomly selected individual without the outcome (24).

Sensitivity analysis

Alongside the univariable and multivariable logistic regression analyses to obtain ORs, Poisson regression with robust standard errors was used to obtain (adjusted) risk ratios (RRs). The dataset included extreme values (two entries ACR=2000 and one entry where ACR=0). Therefore a sensitivity analysis was run to examine the effect of excluding these values.

All analyses were performed in STATA version 12 (StataCorp., College Station, TX,, USA) and the regression models fitted using maximum likelihood estimation.

This was a retrospective study on samples already obtained and the study was approved through the University of Edinburgh and registered with the University of Edinburgh and NHS Lothian on 29/2/2012. No external ethics committee was required. An agreement with the data holder was in place to use the data, for the purposes of this study, which were anonymous and unlinked.

Results

941 pregnant women had an ACR performed during the study period. 224 records were excluded due to predefined exclusion criteria leaving a cohort of 717 women. Complete data (on ACR and existing prognostic factors for the multivariable analysis) was available for 689 women. Women's characteristics are detailed in Table 1. The majority of first ACR measurements were performed between 35 and 40 weeks gestation (interquartile range 35-40 weeks, median=37 weeks and standard deviation= 4 weeks).

Adverse maternal outcomes

204 of 717 included women experienced a composite adverse maternal outcome (28.5%) (Table 2). Thirty women had more than one adverse event (n=174 one event, n=26 two events, n=4 three events) leading to a total of 238 adverse outcomes. Supporting Information Table S1 shows the maternal characteristics for the women with and without composite adverse maternal outcomes. MAP and maternal age at booking were comparable between the two groups. There was no significant difference between the two groups regarding essential hypertension, gestational diabetes, and smoking or social deprivation index. Univariable analysis showed that mean ACR, median gestational age at ACR measurement, mean maternal age, pre-existing diabetes and BMI differ between the two outcome groups (Table S1).

Adverse neonatal outcomes

146 of 717 neonates experienced a composite adverse neonatal outcome (20.4%) (Table 2). Twenty-eight neonates had more than one adverse event (n=118 one event, n=15 two events, n=8 three events and n=5 four events) leading to a total of 192 adverse outcomes. Maternal age was comparable between the two groups. There were differences in median gestational age at ACR measurement, mean ACR, smoking, BMI and MAP between the groups (see Supporting Information Table S2).

Unadjusted and adjusted prognostic value of ACR for maternal and neonatal adverse outcomes

Univariable logistic regression analysis of all 717 women (Table 3) showed that log ACR is prognostic both for maternal (OR 1.52, 95% CI 1.38-1.684) and neonatal (OR 1.13, 95% CI 1.02-1.25) composite adverse outcome. These unadjusted estimates imply that a unit increase in log transformed ACR increases the odds of maternal and neonatal adverse outcomes by 52% and 13% respectively.

Multivariable analysis (based on the 689 women with complete data, Table 3) also showed that log ACR is an independent prognostic factor for maternal composite adverse outcome (OR 1.60, 95% CI 1.43-1.80) and neonatal composite adverse outcome (OR 1.15, 95% CI 1.02-1.29). This implies that a unit increase in log transformed ACR, after adjusting for other factors increases the odds of adverse maternal composite outcome by 60% and adverse neonatal outcome by 15%.

Unadjusted and adjusted prognostic value of ACR for gestation at delivery

Univariable (coefficient -0.38, 95%CI -0.48 to - 0.27, $p<0.001$) and multivariable linear regression (coefficient -0.46, 95% CI - 0.54 to -0.38, p-value <0.001) shows a prognostic effect of log ACR for gestational age at delivery (Supporting Information Table S3). The adjusted estimate implies that for every unit increase in log transformed ACR, the average gestational age at delivery is decreased by about 0.5 weeks.

Discrimination performance of the multivariate models

The apparent C-statistic for the multivariable models was 0.76 (95% CI 0.72-0.80) for composite maternal adverse outcome and 0.72 (95% CI 0.67-0.77) for composite neonatal adverse outcome (Table 3). If ACR is removed then the C-statistic of the multivariable

models reduces considerably to 0.67 (95% CI 0.64-0.72) for maternal composite outcome; however for the neonatal outcome the C-statistic and its 95% CI barely change. This suggests that ACR is more important, in terms of providing additional discrimination to outcome risk predictions, for the maternal outcome.

Sensitivity analysis

Results from the Poisson model with robust standard errors were consistent with those of logistic regression analysis. In both the univariable analysis and multivariable analysis ACR still had significant prognostic ability for maternal (unadjusted RR 1.31, 95% CI 1.24-1.39; adjusted RR 1.32 95% CI 1.25-1.41) and neonatal outcomes (RR 1.10, 95% CI 1.01-1.19; adjusted RR 1.10, 95% CI 1.02-1.19) (Supporting Information Table S4). This implies that, after adjusting for other factors, a unit increase in log transformed ACR increases the risk of adverse maternal outcome by 32% and fetal adverse outcome by 10%.

The sensitivity analysis, excluding the extreme values (ACR=2000 and ACR=0), did not alter any conclusions, for both primary and secondary outcomes (Supporting Information Tables S5 and S6). Figures S1 and S2 show the predicted probability of maternal adverse composite outcomes for ACR (Figure S1) and log ACR (Figure S2) based on the univariable and multivariable models excluding extreme values (ACR=2000 and ACR 0). To illustrate the appropriate fit of a linear relationship between logACR and the log-odds of a maternal composite outcome, Figure 1 shows the unadjusted linear relationship alongside the observed risk.

Discussion

Based on this retrospective cohort study, we show that log ACR is an independent prognostic factor for composite adverse maternal and neonatal outcomes. We suggest that a unit increase in log-transformed ACR is associated with a 30% increased risk of maternal adverse composite outcome and a 10% risk of neonatal adverse composite outcome (corresponding to an increased odds of 60% and 15%, respectively). We also demonstrated that in this population a one unit increase in log ACR was associated with a decrease in gestation at delivery by approximately 0.5 weeks (approximately three days).

Based on the secondary analyses we showed that although ACR is adding prognostic value, the overall discrimination performance of the multivariable models was only moderate. Thus additional prognostic factors are required in order to improve performance further, for a clinically useful model to identify those most likely to have an adverse outcome. In terms of improving discrimination performance (as measured by the C-statistic), ACR appears to be more important for maternal outcomes than fetal outcomes.

A systematic review (25) and study that used ORs and appropriate tests on two ACR thresholds (26) have already indicated a prognostic ability of ACR for adverse outcomes associated with pre-eclampsia. Nonetheless, 3 out of 5 of the studies included in the systematic review (25) were conducted 30 years ago with ACR tests having different thresholds and performed in heterogeneous populations (7). Previous work is also limited by the use of thresholds to categorise (or dichotomise) ACR values (26). Other studies have found the degree of proteinuria not to correlate with adverse outcome (6, 27). A major strength and uniqueness of our study, was that ACR was analysed as a continuous variable (28). . Categorisation of continuous predictors leads to loss of information, hence to loss of power, poor predictive performance and hence poor clinical usefulness (29-31). It also leads to data dredging (to find the 'best' threshold) and does not reflect the underlying prognostic trend.

A log transformation was identified as the most appropriate scale on which to incorporate ACR in the model, suggesting that the effect of a 1-unit increase in ACR depends on the actual value of ACR itself. Other strengths include the use of stored samples to measure ACR using standardised measurement methods; the collection of ACR values blind to the outcome status; the reasonably large cohort itself, and the very small amount of missing data.

This study had some limitations. The primary outcomes were "composite" to increase the power to detect the prognostic ability of ACR. Moreover, the outcomes are objective, and clinical severity is similar within each group. However, it is difficult to examine the effect size of the prognostic factor of interest for each outcome separately (32). It is instead presumed that the effect size is related to all the components of the composite outcome. Recommendations suggest that components of composite outcomes should be considered as secondary outcomes and that the related results are provided alongside primary analysis. This was not possible in this study due to the small number of events in most of the components of

the composite outcome. However, these components were carefully selected to ensure that they were comparable in magnitude of severity and direction of effect.

A further potential limitation results from the retrospective design of our study, as it is difficult to exclude the possibility of intervention bias in observational studies of this type. ACR results were available to clinicians, and may have influenced management decisions and thereby affected maternal and neonatal outcomes. However, these effects are likely to be small, as decision making in women with preeclampsia is based on the whole clinical presentation, not just the amount of proteinuria.

We have shown that in women with suspected pre-eclampsia the ACR at presentation is an independent predictor of adverse outcome. As an indication as to the potential usefulness of ACR in practice, Figure 1 shows how the value of ACR would change the predicted probability of an adverse outcome, for a woman whom otherwise had median values of other covariates included in our model. However, clinical management of women with pre-eclampsia is directed by multiple factors e.g. BP control, haematological and biochemical parameters, symptomatology and fetal considerations including gestation. Thus there is no one single factor that determines management or in particular, intervention via delivery. Our data suggest that ACR should be considered within this clinical assessment.

A recent series on prognosis research (9-12) discusses how a single prognostic factor (such as ACR) rarely predicts individual outcome risk accurately, and usually does not suitably discriminate between high risk and low risk individuals. This is why prognostic models are needed, as they utilize multiple prognostic factors in combination to improve individual risk prediction accuracy and to better discriminate the underlying risk across individuals (33). Future work should focus on identifying further independent prognostic factors for adverse outcomes, to further improve the discrimination performance of prognostic models. This may include the examination of the prognostic value of multiple measurements of ACR over time. In due course, a prognostic model could be developed incorporating a large set of prognostic factors (including ACR), followed by internal and external validation to ensure reliability of the model predictions. At that stage, its use in clinical decision making could be evaluated, for example based on values of high predicted risk that warrant clinical action.

Funding

There was no funding for this study. SJS and FD are supported by Tommy's (registered charity no 1060508 and SCO39280), who contribute to research infrastructure costs.

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Supporting Information legends

Table S1: Maternal characteristics for women who experienced maternal adverse composite outcome, values are numbers and percentages unless otherwise stated.

Table S2: Maternal characteristics for neonatal who experienced adverse composite outcome,

values are numbers and percentages unless otherwise stated.

Table S3: Linear regression results for the unadjusted and adjusted model for the secondary outcome; gestational age at delivery.

Table S4: Poisson regression with robust SE results for ACR (log transformed) for unadjusted, adjusted models, where the response is composite maternal/neonatal adverse outcome.

Table S5: Logistic regression results with extreme ACR values removed for log transformed ACR for unadjusted and adjusted models for the primary outcomes: composite maternal adverse outcome and composite neonatal outcome.

Table S6: Linear regression results with extreme ACR values removed for log transformed ACR for the unadjusted and adjusted model for the secondary outcome; gestational age at delivery.

Figure S1: Graph of the predicted probability of maternal composite adverse outcome (AO) against albumin [mg/L] creatinine [mmol/L] ratio (ACR). The adjusted (red) and unadjusted (blue) models were fitted using log transformed ACR and the logit was obtained using the coefficients from the fitted model multiplied by the means/medians of all other continuous adjustment factors, the most common category of the categorical adjustment factors and the values of log ACR.

Figure S2: Graph of the predicted probability of maternal composite adverse outcome (AO) against the log transformed albumin [mg/L] creatinine [mmol/L] ratio (ACR). The adjusted (red) and unadjusted (blue) models were fitted using log transformed ACR and the logit was obtained using the coefficient of log ACR from the fitted model multiplied by the values of log ACR.

Table and figure legends

Table 1: Baseline maternal characteristics (values are numbers and percentages at the presence of a given characteristic).

Table 2: Number of maternal and neonatal adverse outcomes.

Table 3: Logistic regression results for unadjusted and adjusted models for the primary outcomes: composite maternal and composite neonatal outcomes.

Figure 1. Graph of the predicted probability of maternal composite adverse outcome against albumin [mg/L] creatinine [mmol/L] ratio (ACR). The adjusted (red) and unadjusted (blue) models were fitted using loge (ln) transformed ACR and the logit was obtained using the coefficients from the fitted model multiplied by the means/medians of all other continuous adjustment factors, the most common category of the categorical adjustment factors and the values of log ACR.

Table 1: Baseline maternal characteristics (values are numbers and percentages at the presence of a given characteristic)

Characteristic	**Participants (N=717)**
Maternal age at delivery (years), mean (SD)	29.93 (6.06)
Booking Characteristics: -	
Nulliparity	57.18%
Essential hypertension	9.34%
Pre-existing diabetes	2.79%
Current smoker	15.85%
Scottish Index of Multiple Deprivation:	
1 (most deprived)	21.51%
2	22.63%
3	20.39%
4	15.39%
5 (least deprived)	20.11%
Body mass index:	
<18.5	2.32%
18.5-24.99	33.48%
25.0-29.99	28.55%
30.0-34.9	20.14%
35.0-39.9	9.71%
>40	5.80%
Booking systolic BP, mean (SD)	115.26 (12.48)
Booking diastolic BP, mean (SD)	69.78 (9.81)
Booking mean arterial BP, mean (SD)	84.94 (9.95)
Development of Gestational Diabetes	3.35%
Gestational age at ACR test (weeks), median (IQR)	37.43 (35.0-39.14)
ACR result (mg/mmol), median (IQR)	4.40 (1.40-23.60)
Gestational age at delivery (weeks), median (IQR)	39.43 (38.00-40.43)

Abbreviations: SD standard deviation, IQR interquartile range; BP blood pressure; HDU high dependency unit; ICU intensive care unit; HELLP hemolysis elevated liver enzymes low platelet count syndrome

Table 2: Number of maternal and neonatal adverse outcomes

Maternal adverse outcomes (Total n=238)	**Values are numbers**
Use of magnesium sulphate	12
Use of intravenous antihypertensives	15
Admission to HDU or ICU for hypertension	196
Abruption	7
Eclampsia	0
HELLP	8
Neonatal adverse outcomes (Total n=192)	
Iatrogenic preterm delivery < 34 weeks	33
Birth weight <5th centile	98
Abnormal Dopplers (AEDF or REDF)	11
Arterial cord pH < 7.1	12
Need for ventilation	32
Intrauterine death	5
Neonatal death	1

Abbreviations: HDU high dependency unit; ICU intensive care unit; HELLP hemolysis elevated liver enzymes low platelet count syndrome, AEDF absent end-diastolic flow; REDF reversed end-diastolic flow.

Table 3: Logistic regression results for unadjusted and adjusted models for the primary outcomes: composite maternal and composite neonatal outcomes

		Composite maternal adverse outcome			Composite neonatal adverse outcome		
Model	**Variable**	**OR (95% CI)**	**p value**	**ROC***	**OR (95% CI)**	**p value**	**ROC***
unadjusted	ACR**	1.52 (1.38 - 1.68)	<0.001	0.70 (0.66 - 0.74)	1.13 (1.02 - 1.25)	0.022	0.557 (0.504 - 0.610)
adjusted	ACR**	1.60 (1.42- 1.80)	< 0.001	0.76 (0.72 - 0.80)	1.15 (1.02 - 1.29)	0.025	0.718 (0.668 - 0.760)
	gestational age at ACR	0.88 (0.83 - 0.92)	< 0.001		0.25 (0.16 - 1.29)	< 0.001	
	maternal age	1.04 (1.08 - 1.08)	0.019		0.99 (0.95 - 1.02)	0.505	
	essential hypertension	0.78 (0.38 - 1.60)	0.505		1.62 (0.79 - 3.33)	0.19	
	pre-existing diabetes	0.68 (0.12 - 3.72)	0.655		1.77 (0.40 - 7.88)	0.452	
	gestational diabetes	1.02 (0.38 - 2.77)	0.964		0.73 (0.19 - 2.77)	0.64	
	smoking	0.85 (0.50 - 1.45)	0.55		1.94 (1.16 - 3.26)	0.012	
	nulliparity	0.96 (0.66 - 1.40)	0.826		1.16 (0.77 -1.75)	0.471	
	social deprivation index						
	1	1			1		
	2	0.80 (0.46 - 1.41)	0.451		0.95 (0.53 - 1.72)	0.876	
	3	1.10 (0.63 - 1.92)	0.73		0.78 (0.42 - 1.45)	0.437	
	4	0.623 (0.33 - 1.19)	0.152		0.78 (0.39 - 1.55)	0.473	
	5	0.424 (0.26 - 0.80)	0.008		0.84 (0.43 - 1.62)	0.603	
	body mass index						
	< 18.5	1			1		
	18.5 -24.99	1.06 (0.32 - 3.50)	0.93		0.21 (0.07 - 0.64)	0.006	
	25.0 - 29.99	1.47 (0.44 - 4.93)	0.535		0.12 (0.04 - 0.38)	< 0.001	
	30.0 - 34.9	0.70 (0.20 - 2.48)	0.581		0.11 (0.03 - 0.37)	< 0,001	
	35.0 - 39.9	0.50 (0.13 - 1.98)	0.321		0.16 (0.04 - 0.57)	0.005	
	> 40.0	0.56 (0.13 - 2.39)	0.434		0.09 (0.02 - 0.41)	0.002	
	mean arterial blood pressure	1.02 (1.00 - 1.05)	0.041		0.99 (0.97 - 1.01)	0.381	

ROC receiver operating characteristic; * C statistic; ** log transformed ACR (albumin creatinine ratio)