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serum creatinine distribution

can predict adverse pregnancy outcomes

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Gestational age-specific

serum creatinine distribution

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Directed by Professor Seong Jin Choi

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I respectfully dedicate this dissertation to my mother and father, who have provided me with their unconditional love throughout the life.

I will always remember my blessings. Thank you.

Jieun Kang

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ABSTRACT

Gestational age-specific serum creatinine distribution can predict adverse pregnancy outcomes

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Directed by Professor Seong Jin Choi

Serum creatinine level (SCr) typically decreases during pregnancy due to physiologic glomerular hyperfiltration. Therefore, the clinical practice of estimated glomerular filtration rate (eGFR) based on SCr concentrations might be inapplicable to pregnant women with kidney disease since it does not take into account of the pregnancy-related biological changes. We integrated the Wonju Severance Christian Hospital (WSCH)-based findings and prior knowledge from big data to reveal the relationship between the abnormal but hidden SCr level and adverse pregnancy outcomes. We analyzed 4,004 pregnant women who visited in WSCH. Adverse pregnancy outcomes included preterm birth,

preeclampsia, fetal growth retardation, and intrauterine fetal demise. We categorized the pregnant women into four groups based on the gestational age (GA)-unadjusted raw distribution (Q1-4raw), and then GA-specific (Q1-4adj) SCr distribution. Linear regression analysis revealed that Q1-4adj groups had better predictive outcomes than the Q1-4raw groups. In logistic regression model, the Q1-4adj groups exhibited a robust non-linear U-shaped relationship with the risk of adverse pregnancy outcomes, compared to the Q1-4raw groups. The integrative analysis on SCr with respect to GA-specific distribution could be used to screen out pregnant women with a normal SCr coupled with a decreased renal function.

Ⅰ. INTRODUCTION

Pregnancy is known to cause physiological alterations, including blood volume expansion via increased cardiac output and decreased systemic vascular resistance[1,2]. Specifically, systemic vasodilation and glomerular hyperfiltration are normal hemodynamic adaptations in pregnancy[1].

As gestational age (GA) increases, the glomerular filtration rate (GFR) during pregnancy increases physiologically, and the serum creatinine level decreases[3]. The currently used GFR estimation formula based on blood creatinine concentrations cannot be accurately applied in pregnant women[4,5].

The Modification of Diet in Renal Disease (MDRD) formula[4], which estimates GFR using a combination of serum markers and clinical parameters, has become a standard clinical method to estimate renal function in patients with chronic kidney disease (CKD). The feasibility of using this formula in the pregnant population has not been well studied, and guidelines on application of the MDRD formula specifically exclude interpretation in pregnant women[5,6]. Hence, it can be interpreted as a normal reference range for pregnant women with abnormal kidney function because it does not reflect normal physiological changes during pregnancy[5]. This makes it difficult to diagnose early and provide proper treatment for complications that can affect both fetuses and mothers[7].

The incidence of CKD increases with pregnancy at advanced maternal ages[2]. Women with renal disorders face several problems in pregnancy due to increased physiologic changes accompanying renal dysfunction, including risk for disease progression, the potential teratogenicity of medications, and the increased risk of complications such as preeclampsia and preterm delivery[2,8-10]. Therefore, it is important to accurately evaluate renal function during pregnancy[11].

Pregnancy status in CKD patients is known to be related with adverse pregnancy outcomes, such as preeclampsia[12] and premature delivery[13,14]. Pregnant women diagnosed with CKD were typically categorized into three groups based on the severity of kidney dysfunction: mild (SCr<1.5 mg/dL), moderate (1.5-2.5 mg/dL), and severe (>2.5 mg/dL)[14]. However, Smith et al.[5] suggested that the sole application of serum creatinine (SCr) concentration or SCr-based equations tend to substantially underestimate renal function during pregnancy. The Torino-Cagliari Observational Study[15] found that the risk of adverse pregnancy outcomes increases stepwise as CKD stage 1 transitions to stages 4-5. However, the risk of adverse pregnancy outcomes was not significantly different between pregnant CKD stage 1 patients and normal pregnant women[5]. Multidisciplinary expert groups in Seoul National University focused on GFR estimated by midterm SCr to identify the association between kidney function and adverse pregnancy outcomes[9].

Our study had two main tasks. First, we integrated an automatic platform and a manual method to establish a dataset on pregnant

women. The automatic work was performed by a laboratorian, a computer scientist, and a database administrator, and the manual task was performed by domain experts, including an obstetrician and a family medicine doctor. Second, we implemented prior knowledge[16] to improve the predictive power of adverse pregnancy outcomes. Recently, Harel, Ray and their colleagues[8,16] collected approximately 362,000 measurements of SCr levels from 243,534 women, and established the GA-specific distribution. In this study, we applied the previously validated findings to identify the association between kidney function and adverse pregnancy outcomes.

Ⅱ. METHODS

2.1 Data collection.

We performed a retrospective study on pregnant women giving birth between January 2010 and December 2020 at the Wonju Severance Christian Hospital (WSCH). Eligible subjects were women who had a singleton birth at more than 20 weeks gestation and were aged 16–50 years at the time of delivery. We constructed the initial dataset with the above criterion (i.e., 20 weeks and age) by database administrator as our previous work[29]. Afterward, we selected pregnancy cases based on patients' case notes that had been manually recorded by the department of Obstetrics and Gynecology. We excluded pregnant women that did not have data for SCr levels and SCr measurement times.

The present study was approved by the Institutional Review Boards (IRB) of WSCH (CR321084). This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was an observational study without medical intervention, so the need to obtain informed consent from patients was waived. The waiver of informed consent was also confirmed by the above IRB of WSCH (CR321084).

2.2 Adverse pregnancy outcomes.

Several studies have analyzed the association between kidney function and adverse pregnancy outcomes[8,16]. Park et al.[7] defined pregnancy outcomes as being adverse when a pregnant woman has one or more of the following : Preterm Birth (PTB), low birth weight, or preeclampsia. Harel et al.[14] selected extreme PTB, preeclampsia, perinatal mortality, and severe fetal growth restriction (FGR) as the main adverse pregnancy outcomes. Motivated by these studies, we determined PTB (delivery before 37 weeks gestation), preeclampsia (blood pressure$\geq$140/90 with significant proteinuria and/or end organ damage), FGR (birth weight below 10th percentile adjusted for gestational age), and intrauterine fetal demise (IUFD) as adverse pregnancy outcomes.

2.3 Covariates.

Harel et al.[8] determined maternal age, rural residence, region of origin, gestational week, preconception SCr, chronic diseases (diabetes and hypertension), and tobacco/illicit drug (each$\leq$years before conception) as covariates. Park et al.[7] selected age, BMI, weight gain until delivery, hypertension, diabetes, hypertensive disorder during pregnancy, previous history of stillbirth/miscarriage, multiparity, and hospitalization status. Motivated by these studies, we categorized the parity type into two groups: nulliparity and multiparity. For underlying maternal diseases, hypertension and diabetes were included in this

study, which were determined only by diagnosis code (i.e., ICD10) due to lack of data pertaining to blood pressure or serum fasting glucose at the time of SCr measurement. SCr measurement was performed using the Cobas® 8000 system (Cobas® c 702 and e 601 module; Roche Diagnostics, Switzerland).

2.4 Statistics.

Continuous and categorical variables were analyzed according to the four groups categorized by the GA-specific SCr distribution[16] using one-way analysis of variance (ANOVA) and Chi-square test, respectively. To test for linear trends of categorical or continuous variables, we determined the median SCr levels of each group as continuous variables in the Chi-square test and one-way ANOVA. All statistical analyses and graphic works were performed using R software (version 4.0.1, the R Foundation). A two-sided p value less than 0.05 was considered to indicate statistical significance for all analyses.

III. RESULTS

3.1 Determination of SCr group based on the GA-specific SCr distribution.

We analyzed 4,004 pregnant women who visited WSCH during the study period. For the 4,004 subjects, 10,126 measurements of SCr levels existed, indicating that a person had an average of 2.53 times of SCr evaluations. In most cases (n=1942), the SCr was measured once; it was measured 23 times in two cases and 24 times in one case (Fig. 1). For patients with multiple SCr measurements, we used the maximum estimated value of SCr level.
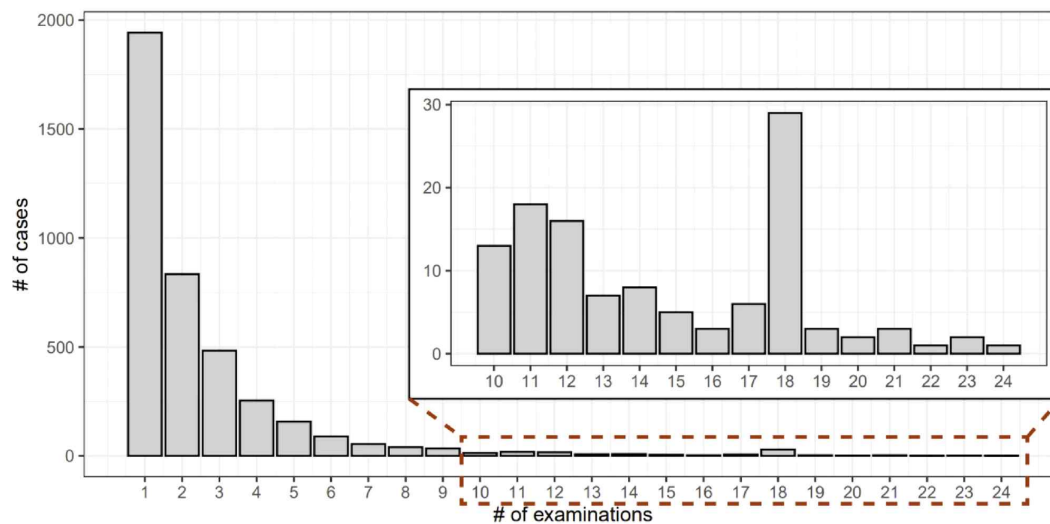

Figure 1. The number of cases according to the number of examinations performed to determine serum creatinine levels.

We used two methods for grouping all pregnancies based on the level of SCr (Fig. 2). At first, we divided SCr into four groups based on the 25th, 50th, and 75th percentile of SCr levels (Fig. 2A), thereby, 1,097, 978, 955, and 974 subjects were evenly grouped into four raw groups by SCr levels [quartile(Q)1raw to Q4raw, respectively]. For the other method, we grouped all SCr results according to the distribution of GA-specific SCr levels, as proposed by Harel and colleagues[16]. In detail, we mapped our SCr results onto this distribution that includes GA and SCr levels as X and Y axes, respectively (Fig. 2B). As a result, 1,888, 813, 835, and 468 subjects were arranged into four groups [Q1adj(an adjusted group by GA-specific Scr distribution) to Q4adj, respectively].
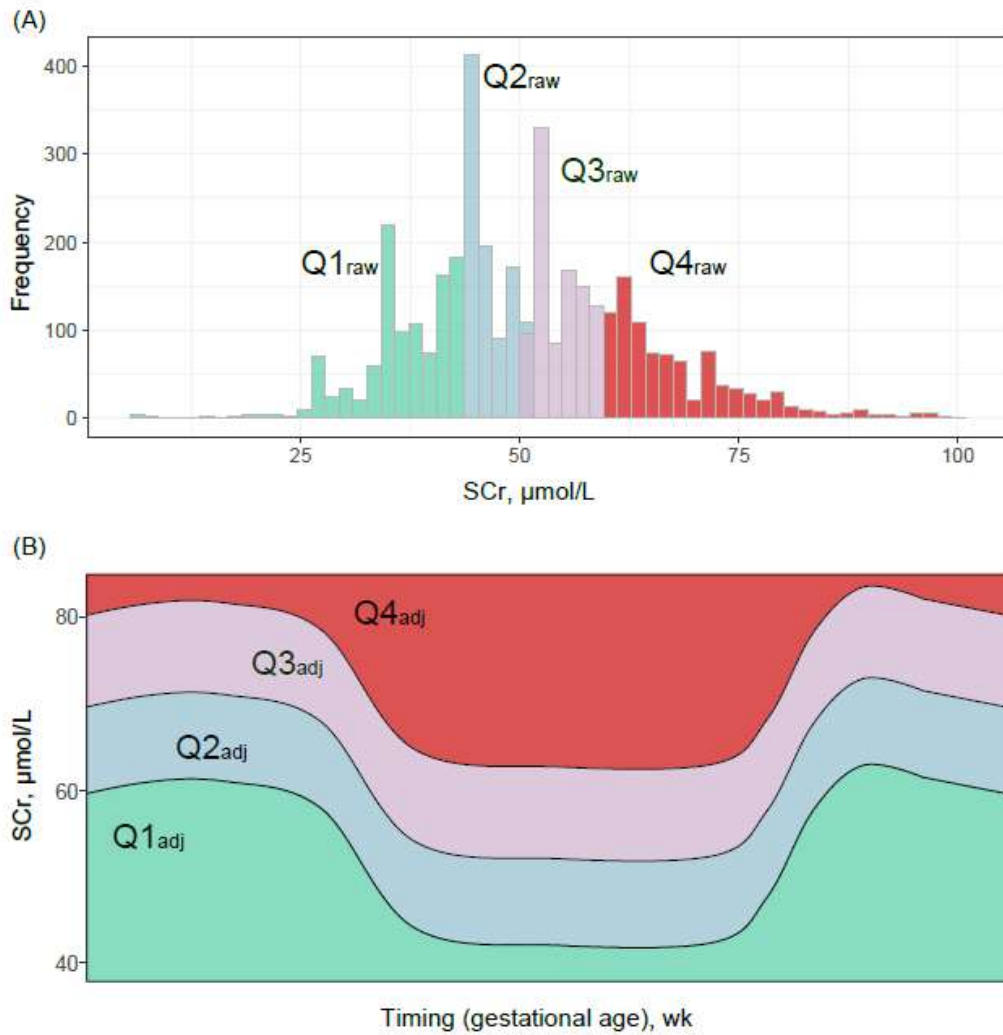
Figure 2. Figure shows the two methods used to categorize the subjects into four groups based on the levels of serum creatinine (SCr). (A) Figure shows the distribution of our original or raw data. (B) Figure shows the abstract version of the distribution of gestational age-specific serum creatinine made by Harel et al[16].

3.2 Medical and biochemical characteristics.

General characteristics, including medical and biochemical data based on the four SCr groups determined by the GA-specific SCr distribution[16] are summarized in Table 1. The average SCr levels showed a stepwise increase as it transitioned from the Q1adj to Q4adj group. The mean age was lowest in Q1adj group, but did not significantly differ among Q2adj to Q4adj groups (Table 1). The subjects in the Q4adj group had the following characteristics when compared to the Q1adj group : high ratio of multi-para, diabetes, PTB, preeclampsia, and FGR (Table 1).

	Q1$_{adj}$	Q2$_{adj}$	Q3$_{adj}$	Q4$_{adj}$	P for trend
n	1,888	813	835	468	
SCr, μmol/L	41±0.17	52.8±0.17	60.1±0.2	86.2±3.1	<0.001
SCr raw groups, n					
Q1$_{raw}$	1097 (58.1)	0 (0)	0 (0)	0 (0)	
Q2$_{raw}$	663 (35.1)	298 (36.7)	17 (2)	0 (0)	
Q3$_{raw}$	121 (6.4)	423 (52)	402 (48.1)	9 (1.9)	
Q4$_{raw}$	7 (0.4)	92 (11.3)	416 (49.8)	459 (98.1)	
Age, year	32.6±0.12	33.2±0.17	33.6±0.18	33.6±0.23	<0.001
Parity type					
Nulliparity, n	974 (51.6)	361 (44.4)	324 (38.8)	165 (35.3)	<0.001
Multiparity, n	914 (48.4)	452 (55.6)	511 (61.2)	303 (64.7)	<0.001
Hypertension, n	10 (0.5)	7 (0.9)	18 (2.2)	8 (1.7)	0.001
Diabetes, n	17 (0.9)	21 (2.6)	29 (3.5)	16 (3.4)	<0.001
Adverse pregnancy outcomes					
Preterm birth	918 (48.6)	302 (37.1)	371 (44.4)	280 (59.8)	<0.001
Preeclampsia	59 (3.1)	53 (6.5)	93 (11.1)	112 (23.9)	<0.001
FGR	304 (16.1)	145 (17.8)	176 (21.1)	144 (30.8)	<0.001
IUFD	57 (3)	12 (1.5)	17 (2)	18 (3.8)	0.026
Number of adverse pregnancy outcomes					
0	721 (38.2)	364 (44.8)	322 (38.6)	125 (26.7)	
1	906 (48)	320 (39.4)	332 (39.8)	159 (34)	
2	231 (12.2)	103 (12.7)	136 (16.3)	109 (23.3)	
3	28 (1.5)	22 (2.7)	42 (5)	72 (15.4)	
4	2 (0.1)	4 (0.5)	3 (0.4)	3 (0.6)	

Table 1. Medical and biochemical characteristics based on SCr groups categorized by the gestational age specific serum creatinine distribution made by Harel and colleagues[16]. SCr serum creatinine, FGR fetal growth retardation, IUFD intrauterine fetal demise.

3.3 Associational patterns of two grouping methods based on different SCr distributions with adverse pregnancy outcomes.

The SCr groups stratified based on raw SCr distribution (Q1raw–Q4raw) could reflect the adverse pregnancy outcomes. In detail, the number of cases with two or more adverse pregnancy outcomes significantly increased from Q1raw to Q4raw. However, the ratio of cases with two or more number of adverse pregnancy outcomes increased gradually from Q1raw to Q3raw, but drastically from Q3raw to Q4raw (Fig. 3A). The four groups made by the GA-specific SCr distribution showed a more gradual pattern of increase in cases with an adverse pregnancy outcomes (Fig. 3B), compared to the original SCr distribution. For the cases with two or more adverse outcomes, two grouping methods showed a well-characterized stepwise increase pattern (Fig. 3A,B). In uni- or multivariate linear regression (LiR) with SCr group and the number of adverse pregnancy outcomes set as independent and dependent variables, the GA-specific SCr group had high beta-coefficients and low p-values, compared to the groups determined by the original SCr distribution (Fig. 3C).
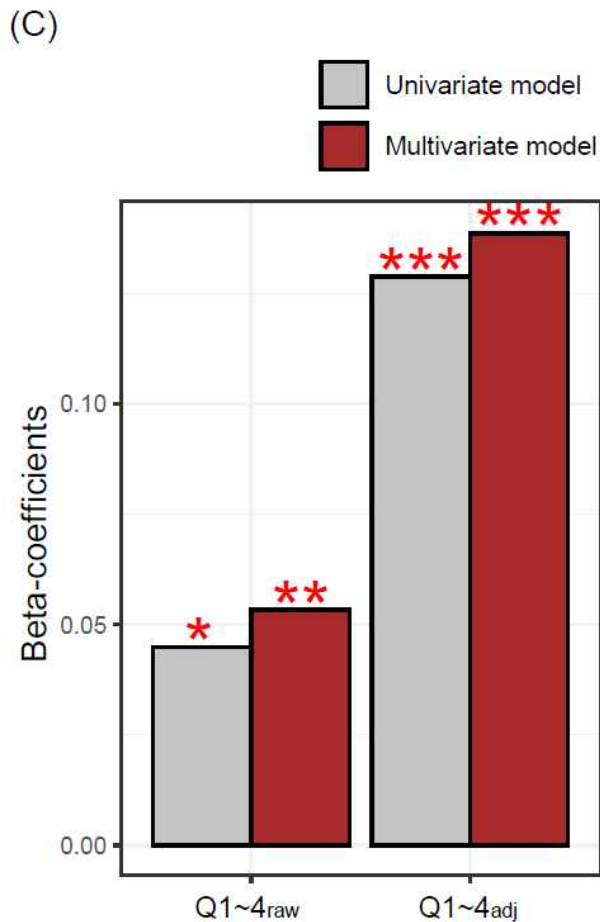
(A)

(B)

(C)
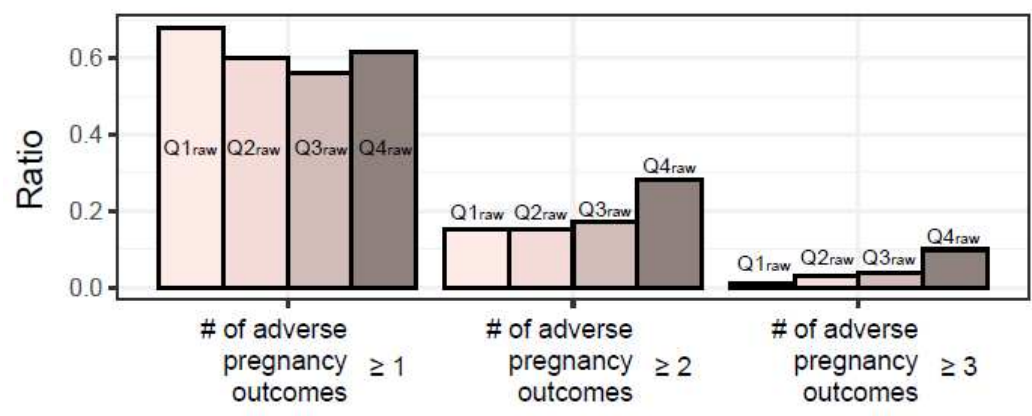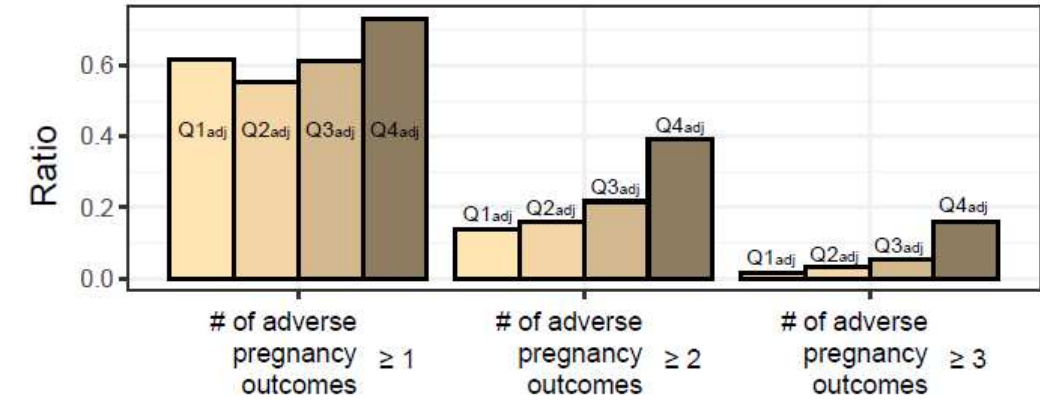
Figure 3. Association between SCr groups and the number of adverse pregnancy outcomes. **(A,B)** Adverse pregnancy outcomes include preterm birth, preeclampsia, fetal growth retardation, and intrauterine fetal death; therefore, the maximum value of the number of pregnancy outcomes is four. **(C)** Y-axis indicates beta-coefficients obtained from linear regression with the number of adverse pregnancy outcomes and SCr groups (Q1-4raw or Q1-4adj) set as dependent and independent variables, respectively. Age, hypertension, diabetes, and parity types are covariates for multivariate models. *, **, *** indicate p value<0.001,<0.00001,<0.0000001, respectively.

We re-grouped all subjects into two groups (with or without an adverse pregnancy outcomes), then conducted uni- or multivariate logistic regression (LR) considering the binary status (adverse pregnancy outcomes vs. control) and quartile group of SCr (Q1-Q4raw or Q1-Q4adj) as dependent and independent variables, respectively. Both original and GA-specific SCr distributions had non-linear U shaped associations with adverse pregnancy outcomes, but the results in Q3raw and Q4raw showed insignificant results (Fig. 4A). The GA-specific SCr groups showed a significant U-shaped relationship with the risk for adverse pregnancy outcomes (Fig. 4A). The relational pattern between SCr and PTB was similar with that of all types of adverse pregnancy outcomes (Fig. 4B). In cases of preeclampsia and FGR, the SCr level exhibited a monotonic increasing pattern of relationship (Fig. 4C,D). For intrauterine fetal demise (IUFD), Q1adj and Q4adj had a significantly increased risk (Fig. 4E).
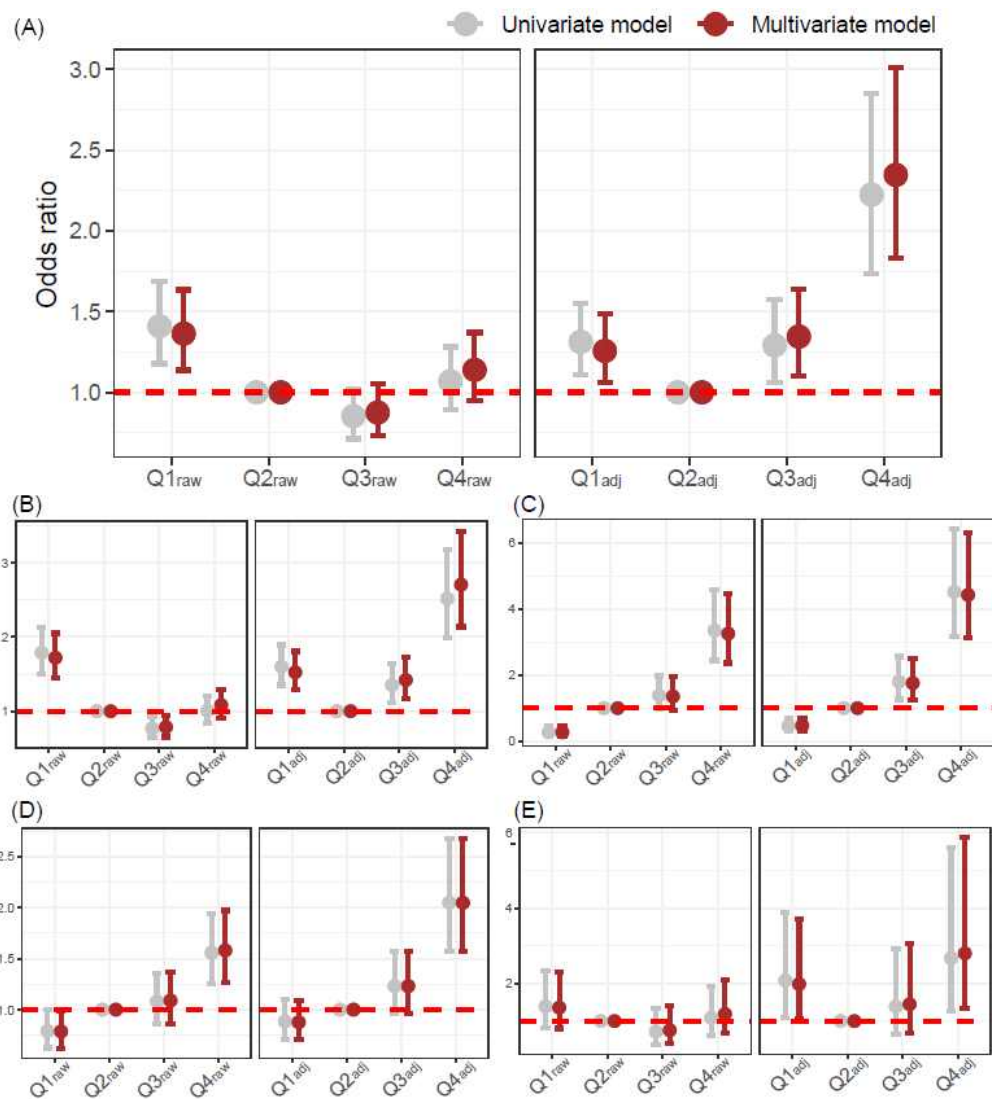
Figure 4. Logistic regression. Q2raw and Q2adj were used as references in all models. Age, hypertension, diabetes, and parity types are covariates for multivariate models. Logistic regression method was used to reveal the relationship between main outcome and four groups based on serum creatinine measurements. Relationship of the four SCr groups with all types of adverse pregnancy outcomes (A), preterm birth (B), preeclampsia (C), fetal growth retardation (D), and intrauterine fetal demise (E) are illustrated.

IV. Discussion

In this retrospective study, we identified that SCr level could predict the risk of adverse pregnancy outcomes as well as the number of co-occurred adverse pregnancy outcomes. Specifically, when using the GA-specific SCr distribution[16], the predictive power of adverse pregnancy outcomes was more robust based on the beta-coefficients and their p-values, compared to the raw SCr distribution (Fig. 3). Moreover, we identified that SCr groups (Q1adj–Q4adj) determined by the GA-specific SCr distribution exhibited a non-linear U-shaped relationship with the risk of adverse pregnancy outcomes. Park et al.[9] reported the convergent findings with our results that midterm GFR had a non-linear relationship with the adverse pregnancy outcomes.

Several studies have pinpointed that exclusively using SCr-based equations could result in the misclassification of kidney function during pregnancy[5,16]. To overcome this limitation, Park et al.[9] only analyzed the midterm GFR values estimated based on SCr levels and their relationship with adverse pregnancy outcomes. Moreover, Harel et al.[16] collected approximately 362,000 SCr results from about 240,000 women and generated the GA-specific SCr distribution. We could not find the GA-specific GFR distribution and could only obtain the GA-specific SCr distribution[16], so we designed the linear regression or logistic regression models based on SCr levels, not GFR values. Direct

application of the findings obtained from the Canadian population to the Korean pregnant women population may yield inaccurate results due to genetic and ethnic differences. However, we considered this distribution to be generalized, and not biased results because it was obtained from over 360,000 results[16]. In addition, it was obvious to provide an improved prediction of the adverse pregnancy outcomes of Korean women when using the Canadian-based distribution. Future studies to curate Korean-specific SCr distribution based on GA are needed. Moreover, it is crucial to establish the GA-specific GFR distribution.

SCr value is dependent on muscle mass or body composition, such as age, sex, and ethnicity. Due to many factors adversely impacting the accurate estimation of GFR, Kidney Disease Improving Global Outcomes(KDIGO) guidelines recommend confirming CKD status in a specific population initially determined based on GFR estimated by SCr (eGFRCr) using an alternative method, such as GFR estimated by serum cystatin C(eGFRcys)[18]. Our study also focused on the inaccurate estimation of kidney function measured by SCr in a specific population (ie, pregnant women), and suggested that the combined information of SCr level and gestational age-specific SCr distribution[16] could improve the prediction of adverse pregnancy outcomes. In pregnancy, albeit kidney hyperfiltration, the maternal serum level of cystatin C is known to be more stable than SCr before the third trimester[19]. Serum level of cystatin C is known to be elevated in the third trimester of pregnancy; however, its underlying

mechanism is not converged[19-21]. In general population, cumulative evidence has supported that eGFRcys is a good alternative method for the GFR estimation, specifically in subgroup exhibiting low muscle amount: elderly population, vegetarians, and those with muscle wasting, chronic disease, or limb amputation[22]. Moreover, most studies commonly suggested that a combined creatinine and cystatin C equation proposed more accurate estimates and greater precision than GFR estimated from creatinine or cystatin C alone[22,23]. Taken together, we suggest that the kidney function of pregnant women is to be measured via multiple serum indices, such as creatinine and cystatin C.

Adverse pregnancy outcomes, such as preeclampsia and PTB, have been considered the leading causes of perinatal morbidity and mortality worldwide[24,25]. Therefore, establishing a prediction model for adverse pregnancy outcomes is crucial to help minimize adverse perinatal outcomes[26,27]. The establishment of the prediction model included two main tasks: one is the feature selection and the other is the optimization of parameters using several machine learning methods[28]. The present study focused on feature selection. Moreover, our results were obtained from previously validated findings[16], also called prior knowledge, indicating that our study analyzed data based on the Bayesian approach or transfer learning[29]. Our findings indicated a non-linear relationship between SCr levels and adverse pregnancy outcomes; therefore, machine learning methods (e.g., support vector machine, random forest, or deep learning)[30] that can deal with data

exhibiting characteristics of the non-linear or complex relationships among features[30] are needed to screen patients with high risk adverse pregnancy outcomes.

In the present study, multidisciplinary experts (i.e., laboratorian, database administrator, obstetrician, and computer scientist) performed multiple tasks to construct a database to identify the risk factors for adverse pregnancy outcomes. Initially, obstetricians are responsible for the literature-based review to select candidate features. Later, laboratorian, database administrator, and computer scientist constructed an initial dataset using the automatic platform, including the candidate variables. Then, the obstetrician and laboratorian manually updated the patient's medical history and pregnancy outcomes.

This study has several limitations. First, because the WSCH is a tertiary hospital, the prevalence of pregnant women with adverse pregnancy outcomes is high compared to general population. To obtain generalized findings, the multi-institutional study or registry is needed, and this study could motivate the multi-center approach. Second, several biomarkers could not be analyzed since the database (e.g., electronic health records and automatic platform) is not designed to compile them. For example, we could not analyze data, such as body mass index (BMI) or waist circumference because they were not recorded at the time of initial pregnancy evaluation. Moreover, due to the retrospective design, we could not control the re-examination of blood tests of pregnant women, resulting that most women examined blood only had a time point of measurement (Fig. 1). Future study that

is reinforced with these limitations could identify the valuable pathophysiological signatures related to decreased renal function and blunted hyperfiltration, and adverse pregnancy outcomes.

We implemented prior knowledge obtained from the enormously large scale of data and observed that elevated SCr levels were significantly related with the risk of adverse pregnancy outcomes. This study is a basic task of developing an algorithm to predict the possibility of adverse pregnancy outcomes based on the pregnant women's SCr levels adjusted by gestational weeks.

Ⅴ. APPENDIX

Case 1. A 35 years woman visited in the department of Obstetrics for the laboratory tests at initial pregnancy evaluation. She had no medical history such as hypertension, diabetes, and CKD. Her GA was 10 weeks and the SCr level was 26.5 μmol/L (0.3 mg/dL) which is within normal range. She measured SCr level at 18 week of GA, showing normal value of 61.9 μmol/L (0.7 mg/dL). We mapped her SCr levels onto GA-specific SCr distribution made by Harel et al.[16], and found that the SCr levels were located in Q1 and Q4 (Fig. 5) indicating a high risk of decreased renal function or blunted hyperfiltration in 18 weeks. She finally exhibited two cases of adverse pregnancy outcomes, including PTB and FGR.

Case 2. A 28 years women visited WSCH for the laboratory tests at the first prenatal encounter. She had no medical history. Her GA was 28.86 weeks and the SCr was measured once and its level was 60.996 μmol/L(0.69 mg/dL) that is normal range. After mapping it onto the GA-specific SCr distribution[16], it was located in Q4(Fig. 5). She finally resulted three cases of adverse pregnancy outcomes, including PTB, preeclampsia, and FGR.
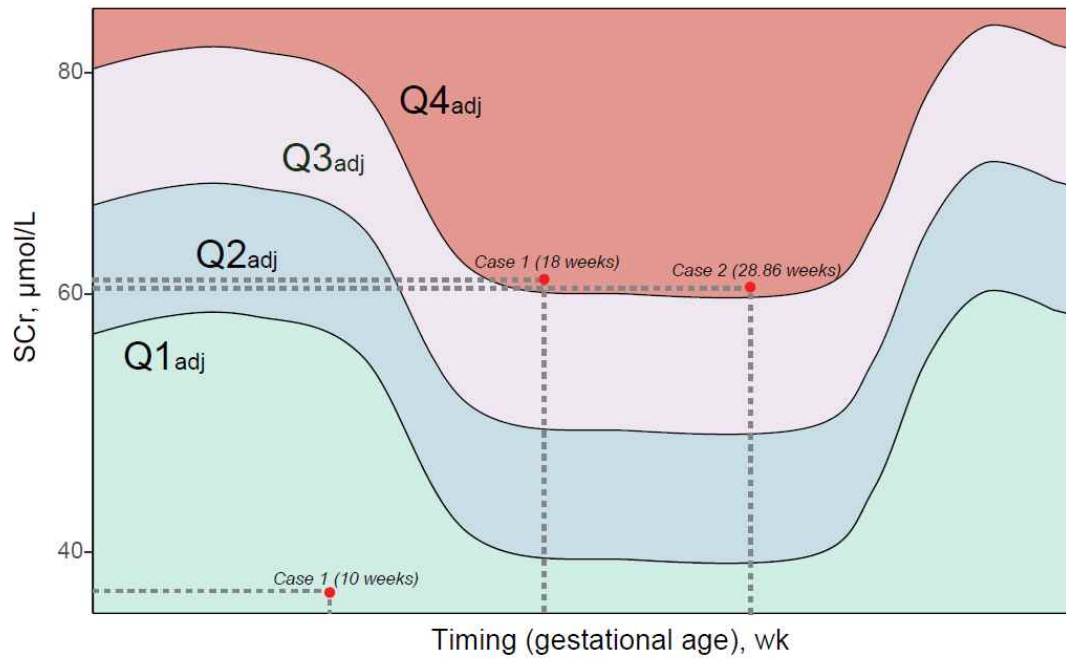
Figure 5. Application of the gestational age-specific serum creatinine distribution in clinical setting

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VII. ABSTRACT IN KOREAN

임신 주 수별 혈청 크레아티닌 분포에 따른
임신 시 합병증 발생의 위험도 예측

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< 지도교수 : 최성진 >

정상 임신 중 산모는 혈장량의 증가와 같은 다양한 생리학적 변화를 겪게 된다. 임신 중 이러한 정상적인 혈류역학적 적응에 따른 사구체 과여과의 결과, 임신 중 혈청 크레아티닌(SCr)의 값은 비임신 시보다 감소한다. 따라서 보편적으로 임상에서 적용하는 혈청 크레아티닌(SCr) 농도를 근거로 계산한 추정사구체여과율(eGFR)은 임신과 연관된 이러한 생리학적 변화들을 고려하지 않으므로, 다양한 혈류역학적 변화들이 생기는 산모들에게 비임신 상태에서와 같은 방식을 적용하기는 어렵다.

본 연구에서는 대규모 집단에서 얻어낸 빅데이터에 기반한 사전지식과 원주세브란스기독병원(WSCH)의 검사결과를 통합해, 정상 수치로 보고되었으나 임신 중 비정상적인 상태로 간주될 수 있는 혈청 크레아티닌 값에 따른 임신 시 합병증 발생과의 관계를 밝혀냈다.

　　원주세브란스기독병원에 방문한 4,004명의 임산부를 대상으로 자료를 분석하였으며, 임신 중 합병증은 조산, 임신중독증, 태아 성장 지연, 자궁 내 태아 사망으로 정의하였다. 임신 주 수를 반영하지 않은 기존의 혈청 크레아티닌 분포(Q1-4raw)와 임신 주 수를 반영한 새로운 혈청 크레아티닌 분포(Q1-4adj)를 기준으로 산모를 각 4개의 군으로 분류했다. 선형회귀 분석에서는 임신 주 수 정보가 반영된 Q1-4adj 군이 Q1-4raw 군보다 임신 중 합병증에 대해 더 나은 예측 결과를 보였다. 로지스틱 회귀 분석에서 임신 주 수 정보가 반영된 Q1-4adj 군은 Q1-4raw 군에 비해 임신 시 합병증의 위험도와 함께 비선형 U자형 관계를 보였다.

　　본 연구에서는 임신 주 수별 혈청 크레아티닌 분포를 반영하여 혈청 크레아티닌 값을 통합적으로 분석할 경우, 신장 기능 저하를 가진 정상 혈청 크레아티닌 값을 가진 산모를 선별하는 데 이용할 수 있음을 제시하고 실제 임상에서의 적용방법과 후속 연구의 방향을 제안하였다.

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주제어 : 과여과, 임신 중 합병증, 임신, 신기능, 신부전, 사구체 여과율, 크레아티닌