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Serum cystatin-c as predictive factor of preeclampsia: A meta-analysis of 27 observational studies

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ABSTRACT

Objective: Serum cystatin-c is a protein that is filtered freely through the glomerulus and reabsorbed and degraded by proximal tubular cells and can be used as a biomarker of renal function. Its levels rise during the third trimester and decrease in the postpartum period. The purpose of the present meta-analysis is to assess the performance of serum cystatin-c for the prediction of preeclampsia.

Design and methods: We used the Medline, Scopus, Clinicaltrials.gov, EMBASE, Cochrane Central Register of Controlled Trials CENTRAL and Google Scholar. We selected all observational studies (both prospective and retrospective) that investigated the accuracy of cystatin-c in predicting preeclampsia. Statistical meta-analysis was performed with the RevMan 5.3 and Stata/IC 13.0 software, using hierarchical models to develop the SROC curve.

Results: The quantitative synthesis was based in 27 studies with a total number of 2,320 women. Serum cystatin-c levels were higher in preeclamptic women compared to healthy pregnant controls (MD: 0.40 mg/l, 95% CI [0.33, 0.46]). The pooled sensitivity of serum cystatin-c for the prediction of preeclampsia was 0.85 (95% CI [0.79–0.89]) and the pooled specificity 0.84 (95% CI [0.77–0.90]. Fagan's nomogram indicated that the post-test probability increased to 14% (positive test) and decreased to 1% (negative test), when the pre-test probability was set at 3%.

Conclusions: According to the findings of our study serum cystatin-c seems to be a promising biomarker for the detection of preeclampsia during the third trimester of pregnancy. Therefore, its implementation in future predictive models in the field is recommended.

1. Introduction

Preeclampsia is a pregnancy-related hypertensive disorder and a major contributor of perinatal morbidity and mortality. Its incidence is estimated approximately at 4.5% of pregnancies, with a wide variance worldwide [1], while its pathophysiology remains still under investigation. It is suggested that poor trophoblast invasion of spiral arteries leads to the release of oxidative and anti-angiogenic factors into the maternal circulation, promoting generalized endothelial damage [2]. Preeclampsia is associated with increased future risk of developing microalbuminuria [3], as well as vascular dysfunction [4], heart failure and death due to cardiovascular disease [5].

Cystatin-C is a 13-kDa cysteine protease inhibitor, produced by all nucleated cells at a constant rate. It is filtered freely through the glomerulus, where it is taken up and degraded by proximal tubular cells. It also presents no tubular secretion and thus it can be used as a candidate biomarker of renal function [6]. Previous studies have shown its effectiveness as a marker for the diagnosis of kidney damage, such as acute kidney injury [7] and renal impairment in diabetic patients [8]. Elevated serum levels of cystatin-c have also been linked with the de development of coronary artery disease, adverse cardiovascular outcomes [9] and all-cause mortality [10].

Normal pregnancy is associated with an increase of serum cystatin-c levels during the third trimester, followed by a significant decrease in the postpartum period [11]. *In vitro* studies have reported that cystatin-c expression is upregulated by extravillous trophoblastic cells in preeclamptic placentae, suggesting its possible interplay during placentation [12]. The role of serum cystatin-c in preeclamptic pregnancies has been investigated by several observational studies during the last decade; however, to date, no consensus exists to suggest its

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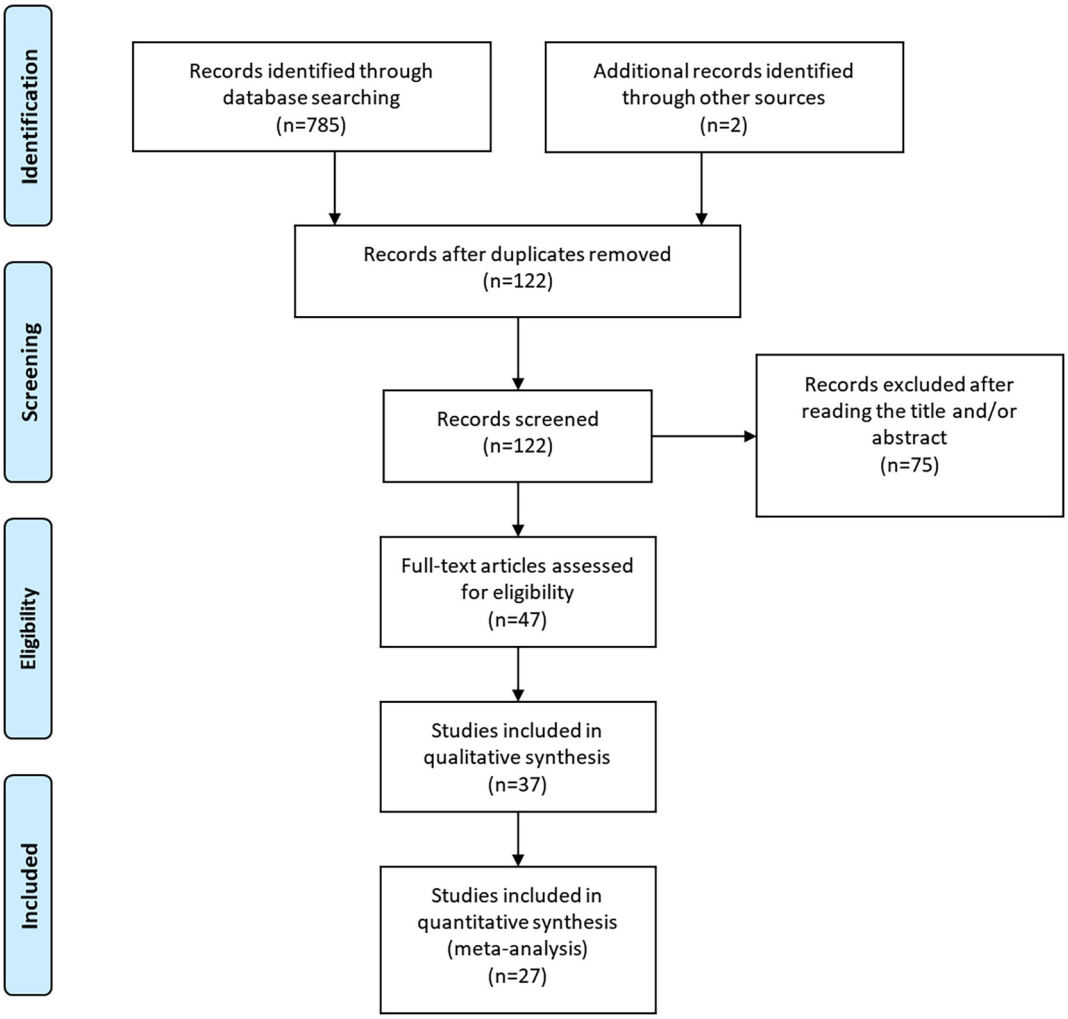

Fig. 1. Search plot diagram.

implementation as screening biomarker in daily practice. The present meta- analysis aims to accumulate, for the first time, current knowledge in the field to determine whether maternal serum cystatin-c concentration is increased in preeclampsia and to evaluate its diagnostic accuracy.

2. Materials and methods

2.1. Study design

The present meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. Eligibility criteria were predetermined by the authors. Language or date restrictions were not applied during the literature research to prevent language bias. The studies were selected in three consecutive stages. The titles and abstracts of all electronic articles were screened to assess their eligibility. The articles that met or were presumed to meet the criteria were retrieved as full texts. In the final stage, all observational (both prospective and retrospective) studies that reported serum cystatin-c levels among preeclamptic and normal pregnant women were selected. Animal studies, case reports and review articles were excluded. Any discrepancies in the methodology, retrieval of articles and statistical analysis were resolved by the consensus of all authors.

2.2. Literature search and data collection

We used the Medline (1966–2018), Scopus (2004–2018), Clinicaltrials.gov (2008–2017), EMBASE (1980–2018), Cochrane Central Register of Controlled Trials CENTRAL (1999–2018) and Google Scholar (2004–2018) databases in our primary search along with the reference lists of electronically retrieved full-text papers. The date of our last search was set at July 31st 2018. The search strategy included the words “cystatin; preeclampsia; eclampsia; gestational hypertension; hypertensive pregnancy; gestosis” and is schematically presented in the PRISMA flow diagram (Fig. 1).

2.3 Definitions

Preeclampsia was defined as a new-onset hypertension (systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg) on at least two consecutive occasions 6 h apart and proteinuria (1+ in urine dipstick or $\geq$300 mg per 24-h urine excretion), appeared after 20 weeks of gestation in a previously normotensive woman. The criteria for diagnosing severe preeclampsia included the presence of blood pressure $\geq$160/110 mmHg and severe proteinuria ($\geq$2+ in urine dipstick or $\geq$5 mg per 24-h urine excretion).

2.4. Quality assessment

The methodological quality of all included studies was assessed

Table 1
Characteristics of included studies.

Author; year	Country	Type of study	Newcastle–Ottawa Scale	Exclusion criteria	Type of sample	Assay method
Preeclampsia vs. control						
Niraula; 2017	Nepal	Cross-sectional	8	Abnormal fetal morphology, gestational age ≤24 weeks, preexisting proteinuria, any other concomitant disease	Serum	PENIA
Vieira; 2017	UK, Australia, New Zealand	Prospective	7	Gestational age < 14 or > 16 weeks, any chronic disease (diabetes, hypertension), multiple pregnancy, preterm birth, fetal abnormalities, any intervention during pregnancy	Plasma	N/A
Saldanha; 2017	India	Case-control	7	Any cardiovascular, endocrine, or renal dysfunction, smoking, gestational age < 37 or > 37 weeks, steroid treatment	Serum	PENIA
Kim; 2017	Korea	Case-control	6	Gestational age < 28 weeks, any chronic disease	Serum	ELISA
Risch; 2017	Switzerland	Nested case-control	8	Gestational age < 11 or > 13 weeks, age < 18 or > 45 years, multiple pregnancy, fetal abnormalities, chronic hypertension, use of anticoagulant or anti-asthmatic drugs, pregnancy after artificial reproductive technologies, spontaneous miscarriage before 24 weeks	Serum	PENIA
Duckworth; 2016	UK, Ireland	Prospective	7	Gestational age < 20 or > 36 weeks, multiple pregnancy (except twin), maternal age < 16 years, any other disease or confirmed preeclampsia	Plasma	Competitive, microtiter ELISA
Singh; 2016	India	Prospective	7	Preexisting hypertension, any other disease (e.g. diabetes, renal disease), multiple pregnancy, eclampsia	Serum	PETIA
Kolialexi; 2015	Greece	Nested case-control	7	Renal dysfunction, proteinuria, gestational age < 11 or > 13 weeks	Serum	ELISA
Malik; 2015	Sudan	Cross-sectional	7	Age < 34 years, absence of preeclampsia, chronic hypertension or gestational hypertension for high risk patients	Serum	PENIA
Dhokikar Gajanan; 2015	India	Case-control	8	Multigravidity, multiple pregnancy, gestational age ≤20 or ≥36 weeks, any other concomitant disease, fetal abnormalities	Serum	PENIA
Beheiry; 2015	Sudan	Case-control	8	Any other chronic disease (e.g. Diabetes, renal disease), multiple pregnancy, abnormal thyroid function, any obstetrical abnormality	Serum	PETIA
Elagwany; 2015	Egypt	Case-control	6	Multigravidity, multiple pregnancy, mild preeclampsia, gestational age < 28 weeks, any concomitant disease	Serum	N/A
Sharma; 2014	India	Case-control	6	Any chronic disease	Serum	PENIA
Isasari; 2014	Indonesia	Cross-sectional	7	Mild preeclampsia, gestational age < 37 weeks, any other disease, multiple pregnancy, pregnant with dead fetus	Serum	PENIA
Xiao; 2013	China	Cross-sectional	6	N/A	Serum	PETIA
Yalcin; 2013	Turkey	Cross-sectional	7	Mild preeclampsia, multiple pregnancy, any infectious disease last month or infiltrative disorders or any other chronic disease (e.g. liver, kidney, autoimmune, malignancy), antihypertensive drugs, smoking, alcohol consumption, oligohydramnios, magnesium prophylaxis	Serum	ELISA
Padma; 2013	India	Cross-sectional	6	History of hypertension, any other chronic disease, gestational age < 28 weeks	Serum	PENIA
Ćebović; 2013	Serbia	Case-control	6	N/A	Serum	PENIA
Guo; 2012	China	Prospective	7	Multiple pregnancy, 1st trimester, any concomitant disease (e.g. hypertension, anemia, heart failure)	Serum	PETIA
Bukan; 2012	Turkey	Case-control	6	N/A	Serum	PENIA
Novakov Mikic; 2012	Serbia	Prospective	6	Any concomitant disease (e.g. renal disease, diabetes), multiple pregnancy, abnormal fetal morphology, gestational age ≥24 weeks	Serum	PETIA
Farag; 2011	Egypt	Case-control	8	Multiple pregnancy, pre-existing diabetes, hypertension, renal disease, 1st or 3rd trimester of gestation	Plasma	ELISA
Saleh; 2010	UK	Case-control	6	1st or 3rd trimester of gestation, any concomitant disease	Serum	PENIA
Rafik Hamad; 2009	Sweden	Case-control	7	Multiple pregnancy, smoking, any chronic disease, in vitro fertilization, egg donation, extreme obesity, antihypertensive treatment	Serum	PENIA
Thilaganathan; 2009	UK	Nested case-control	8	Multiple pregnancy, any other disease, 2nd or 3rd trimester of gestation, history of miscarriage	Serum	PENIA
Franceschini; 2008	Sweden	Case-control	8	Multiple pregnancy, any chronic disease (e.g. diabetes, pre-existing hypertension)	Plasma	ELISA
Lee; 2008	South Korea	Cross-sectional	6	Pre-pregnancy diabetes, hypertension, chronic renal disease, multiple pregnancy	Serum	PENIA
Kristensen; 2007b	Sweden	Case-control	8	Multiple pregnancy, gestational age ≤28 weeks, any other disease	Plasma	PENIA
Yang; 2006	China	Case-control	7	Multiple pregnancy, diabetes mellitus, chronic hypertension, infectious diseases, polyhydramnios, premature rupture of membrane, any other disease	Serum	ELISA

(*continued on next page*)

Table 1 (*continued*)

Author; year	Country	Type of study	Newcastle–Ottawa Scale	Exclusion criteria	Type of sample	Assay method
Herrmann; 2004	Germany	Case-control	8	Chronic hypertension, pre-existing renal or thyroid disease, maternal or fetal infections, fetal abnormalities, drug, alcohol or nicotine abuse	Serum	PENIA
Strevens; 2003	Sweden	Prospective	8	1st or 2nd trimester of gestation, any chronic disease (e.g. diabetes, renal disease)	Serum	PETIA
Strevens; 2002	Sweden	Case-control	7	Gestational age < 28 weeks, history of renal disease	Serum	PETIA
Strevens; 2001	Sweden	Cross-sectional	7	History of renal disease, gestational age ≤ 28 weeks, any drug treatment	Serum	PENIA
Mild Preeclampsia vs. Severe Preeclampsia vs. Control						
Winarto; 2017	Indonesia	Cross-sectional	8	Multiple pregnancy, gestational age ≤ 28 weeks, any chronic disease (e.g. diabetes, renal disease), maternal infection, IUFD	Serum	PENIA
Huang; 2013	China	Retrospective	8	Multiple pregnancy, gestational age < 28 weeks, any maternal or fetal complication	Plasma	PETIA
Gao; 2012	China	Cross-sectional	6	Multiple pregnancy, gestational diabetes, fetal malformations, kidney disease, anemia, any cardiovascular disease	Serum	N/A
Kristensen; 2007a	Sweden	Case-control	7	History of renal disease, hypertension or diabetes, multiple pregnancy	Plasma	PETIA

using the Newcastle-Ottawa Scale (NOS), which evaluates the selection of the study groups, the comparability of the groups and the ascertainment of the exposure or outcome of interest [14]. The studies included in the diagnostic accuracy analysis were further assessed with the QUADAS-2 tool, which consists of 4 domains: patient selection, index test, reference standard, flow and timing [15].

2.5. Statistical analysis

Meta-analysis of the mean difference of cystatin among the various groups was performed with RevMan 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Confidence intervals were set at 95%. The DerSimonian–Laird random effect model was selected to calculate mean differences (MD) and 95% confidence intervals (CI), due to the significant heterogeneity of the methodological characteristics of the included studies (Table 1). Subgroup analysis was conducted based on the severity of the disease. Moreover, to determine possible sources of heterogeneity, univariate meta-regression was performed with Open Meta-Analyst statistical software [16]. Specifically, the effects of study type, type of sample, assay method, region and NOS score were investigated.

The meta-analysis of diagnostic accuracy was performed using hierarchical models with Stata/IC 13.0 (StataCorp. 2017. Stata Statistical Software: Release 13. College Station, TX: StataCorp LLC) using the metandi and midas commands [17,18]. Hierarchical methods are recommended for comparisons of diagnostic accuracy when variability of the thresholds among studies exists, as they jointly analyze sensitivity and specificity. A Fagan's nomogram was used to visualize the association between pre-test and post-test probability according to the likelihood ratio of the test.

2.6. Sensitivity analysis

The influence of individual studies was explored by performing leave-one-out analyses; one study was sequentially omitted at a time in order to find out its effect in the outcome of the meta-analysis using the Open Meta-Analyst software.

3. Results

3.1. Included studies

Thirty-seven studies [12,19–54] were finally included in the present review, with a total number of 6618 women. Among them, 1515 were diagnosed with preeclampsia and 5103 were recruited as healthy pregnant controls. The methodological characteristics and NOS score of each study, along with the patients' eligibility criteria are summarized in Table 1. The characteristics of patients (number, gestational age, maternal age, BMI, systolic blood pressure, serum creatinine and serum uric acid) are presented in Suppl. Table 1. The quantitative synthesis consisted of the meta-analysis of 27 studies [9,12,28–51,53] with a total of 2320 women (1014 preeclamptic, 1306 controls). Ten studies [19–27] were included only in the qualitative synthesis, since they reported their results in terms of median and interquartile range. The meta-analysis of diagnostic accuracy included 12 studies, which provided adequate data to construct the 2×2 table (Suppl. Table 2).

3.2. Excluded studies

Ten studies were excluded after reading the full text [55–63]. Five of them [26,55–57,59] did not report the outcome of interest. Two studies lacked cystatin-c results in a healthy pregnant control group [60,61], while one did not discriminate preeclampsia from gestational hypertension in the patient group [62]. Finally, two studies [63,64] were partial duplicates of studies that were already included in the present review [9,49].

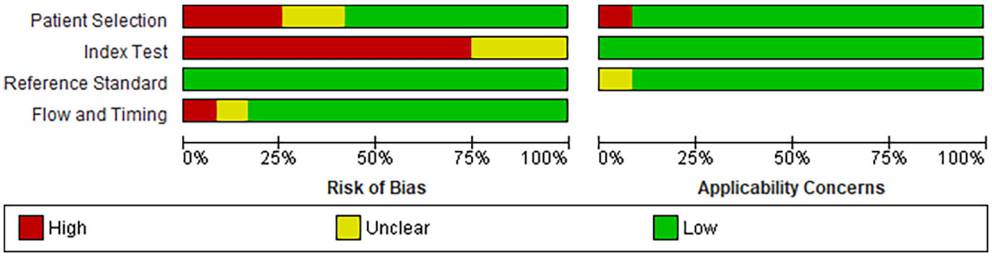

Fig. 2. QUADAS-2 evaluation.

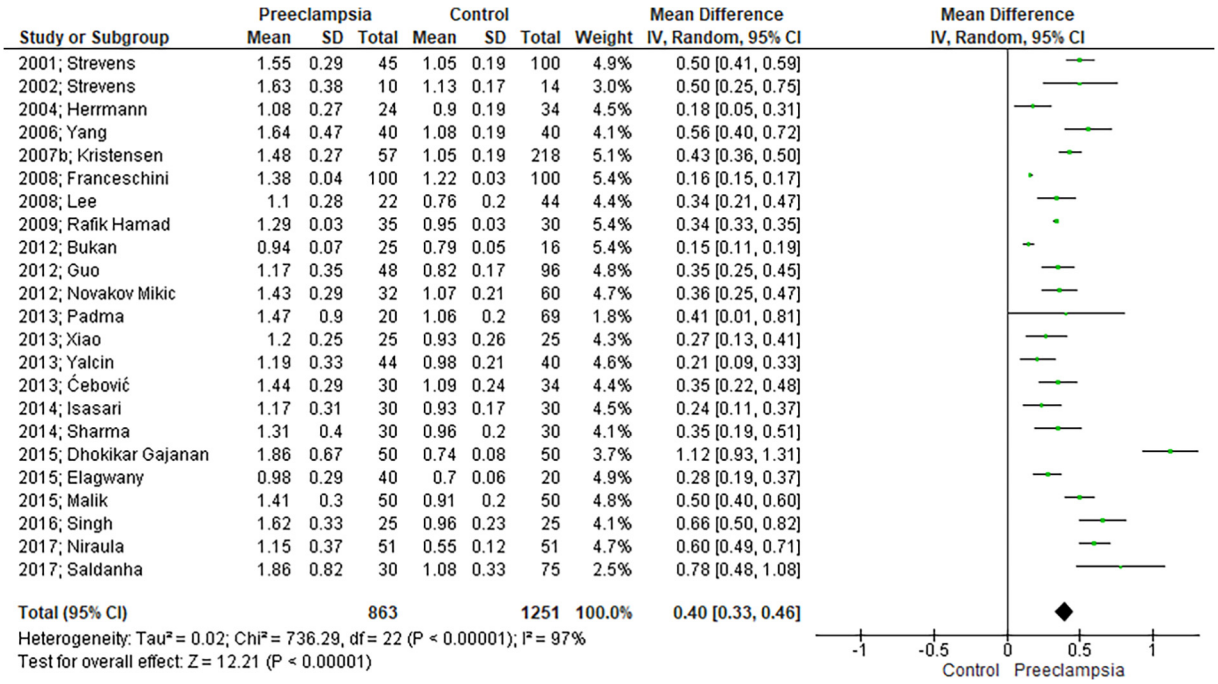

Fig. 3. Mean difference of serum cystatin-c between cases with preeclampsia and healthy controls. The overall result was statistically significant ($p < .001$).

3.3. Quality assessment

The outcomes of the Newcastle-Ottawa Scale are presented in Table 1. As depicted in Fig. 2, the QUADAS-2 tool indicated high risk of bias in the section of index test, since the majority of the included studies did not use pre-specified cut-off values to calculate sensitivity and specificity, but rather preferred to evaluate optimal cut-offs based on their series of patients.

3.4. Qualitative synthesis

The outcomes of the qualitative synthesis are presented in Suppl. Table 3. In nine studies [19,20,22–27], serum cystatin-c levels were significantly elevated in the preeclamptic compared with the healthy pregnant group. In 3 of them [20,23,27] the measurement was made in the 3rd trimester, while in 6 studies [19,22,24–26,41] sampling was performed early in pregnancy. Finally, Duckworth et al. found increased serum cystatin-c in preeclampsia, although the statistical significance of the result was not tested [21].

3.5. Quantitative synthesis

Serum cystatin-c levels were significantly higher in preeclamptic women than in healthy pregnant controls (outcomes from 2114 women, MD: 0.40 mg/l, 95% CI [0.33, 0.46] Fig. 3). The same effect was also observed when cases were classified according to their severity. Specifically, cystatin-c concentration was increased both in mild (161 women, MD: 0.28 mg/l, 95% CI [0.18, 0.38] Suppl. Fig. 1) and severe (370 women, MD: 0.46 mg/l, 95% CI [0.31, 0.60] Suppl. Fig. 2) preeclampsia, when compared with the control group. Moreover, severe cases were significantly associated with higher cystatin-c levels compared to mild ones (191 women, MD: −0.33 mg/l, 95% CI [−0.44, −0.22] Suppl. Fig. 3). The meta-regression (Suppl. Table 4) showed that the examined covariates did not significantly affect study outcomes (*p-value* > 0.05).

The hierarchical summary ROC curve is illustrated in Fig. 4. The estimated sensitivity for the summary point was 0.85 (95% CI [0.79–0.89]) and the specificity was 0.84 (95% CI [0.77–0.90]. The diagnostic odds ratio was calculated at 30.15 (95% CI [16.14–56.29]. The pooled positive likelihood ratio was calculated at 5.36 (95% CI [3.55–8.10]) and the negative likelihood ratio at 0.18 (95% CI [0.12–0.25]). Fagan's nomogram indicated that the post-test probability was increased to 14% (positive test) and decreased to 1% (negative test), when the pre-test probability was arbitrarily set at 3% (Fig. 5).

3.6. Sensitivity analysis

The results of the sensitivity analysis are illustrated in Suppl. Figs. 4–7. The outcomes of the study were stable in the leave-one-out analysis, indicating that no study affected significantly the results of the meta-analysis.

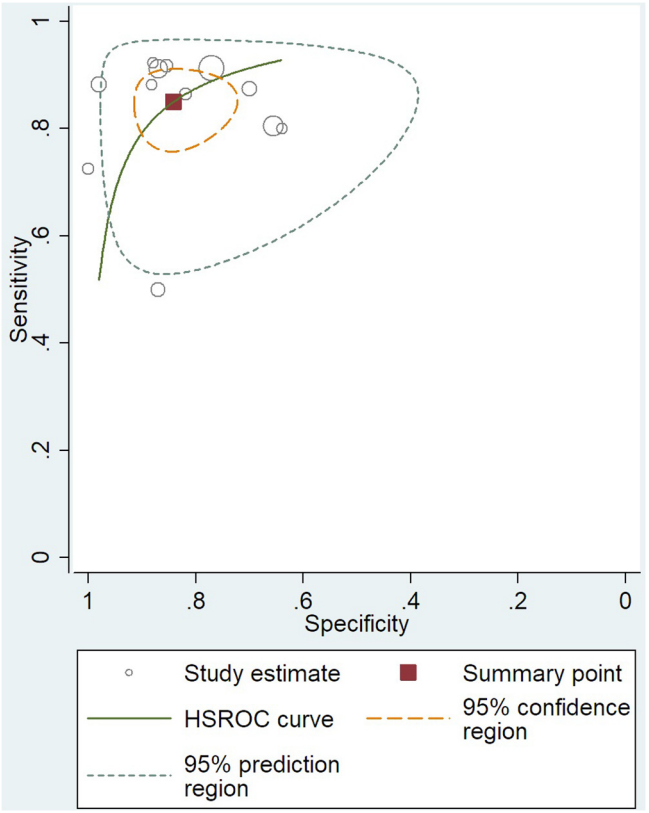

Fig. 4. Hierarchical summary ROC curve (HSROC) for the diagnostic performance of cystatin-c in preeclampsia.

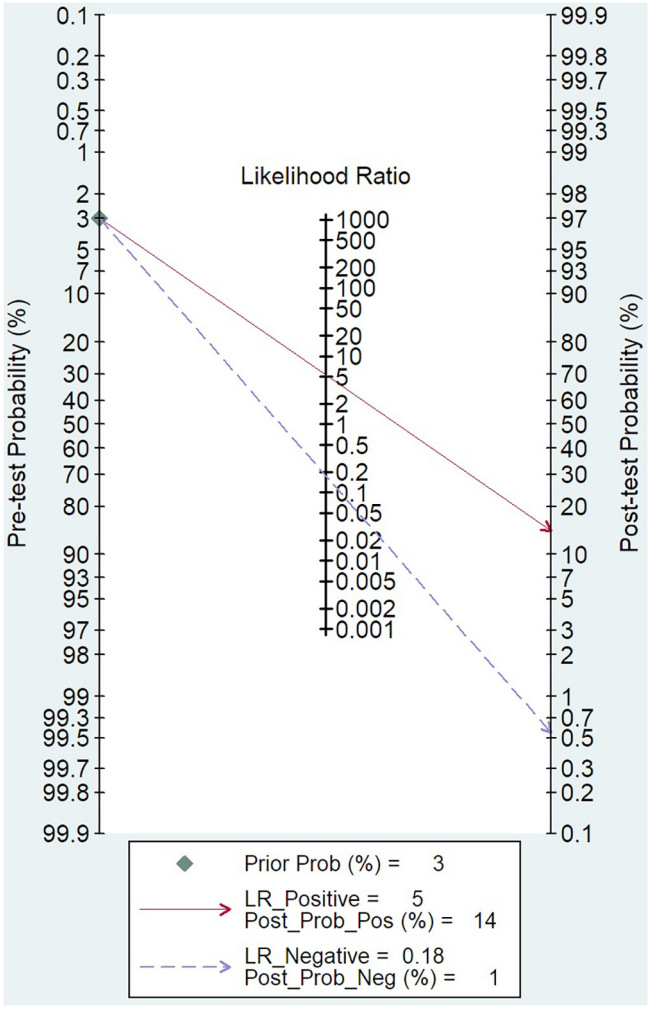

Fig. 5. Fagan's nomogram of pre- and post-test probability. The pre-probability test was set to 3%.

4. Discussion

Preeclampsia is a multisystem disorder with complex pathophysiology. It is a leading cause of maternal and fetal morbidity and mortality [65], and significant effort has been taken to identify women at risk, to improve pregnancy outcomes [66]. The utility of clinical factors alone, such as previous medical and obstetric history, has been proved inadequate in predicting the disease [67]. Although recent research has focused in the investigation of several novel biomarkers, currently there is no effective screening model for preeclampsia [68].

Cystatin-C is a promising index of renal impairment, with predictive value in acute and chronic kidney disease [7,68]. The findings of the present meta-analysis suggest that maternal serum cystatin-c concentration is elevated in preeclampsia and might serve as a useful diagnostic marker, given its sensitivity and specificity (0.85 and 0.84 respectively). Promising data exists about its efficacy early in pregnancy, since 2 studies in the first trimester and 6 studies in the second trimester reported significantly increased cystatin-c values in women that subsequently developed preeclampsia. Its utility as screening tool was mentioned in one study that was excluded from the present meta-analysis [58], which concluded that the combined evaluation of cystatin-c, c-reactive protein and uterine artery resistance index in the second trimester presented adequate predictive accuracy (AUC: 0.825 95% CI [0.743–0.907]). The importance of cystatin-c during the antenatal period as a biomarker of impaired placentation is also supported by two studies that observed its association with fetal growth restriction (FGR) [53], and oxidative stress indices among preeclamptic women [36].

4.1. Strengths and limitations of the study

Our meta-analysis combines for the first time in the literature current knowledge in the field. We aimed to evaluate the impact of potential confounders on observed outcomes with meta-regression and sensitivity analysis and observed that the result remained statistically significant. The statistical analysis was conducted with hierarchical models taking thus account of potential threshold effects. Moreover, a Fagan's nomogram was constructed, providing a tool that estimates the post-test probabilities, according to the calculated likelihood ratios of the test.

Nevertheless, the outcomes of our analysis are based mainly on cross-sectional and retrospective studies that measured cystatin-c levels; hence, the possibility of selection bias is an issue that has to be taken into consideration. Moreover, the evaluation of cystatin-c levels was performed in the third trimester of pregnancy; therefore, its predictive value during the first trimester remains to be determined. Studies did not classify preeclampsia as early or late onset and; thus, it is not possible to know whether its efficacy differs between these two entities. The only available evidence comes from one study [12], reporting that serum cystatin-c was significantly elevated both in early and late-onset preeclampsia cases. Also, studies tended to use optimal cut-offs, which may probably result in an overestimation of the accuracy of the test.

4.2. Implications for current clinical practice and future research

Our meta-analysis suggests that cystatin-c has high diagnostic accuracy and; thus, may serve as a promising candidate for preeclampsia screening. However, certain aspects remain to be explored to draw safe

conclusion about its exact clinical utility. Large-scale prospective cohort studies, with sequential cystatin-c measurements throughout the pregnancy course, are needed to determine the gestational age that would maximize the performance of this biomarker. Cystatin-c thresholds should be pre-specified and cases should be classified in the basis of severity, onset and fetal complications. An economic analysis could, also, help to assess the cost-effectiveness of this test. Finally, future studies should investigate the efficacy of cystatin-c in conjunction with other serum biomarkers and uterine artery Doppler indices, in order to construct an optimal combined model for the prediction of the disease.

5. Conclusion

Cystatin-c seems to be a promising biomarker for the detection of preeclampsia during the third trimester of pregnancy with estimated sensitivity of 85% and specificity of 84%. Its implementation in future predictive models is, therefore, strongly recommended. However, current data are based on third trimester measurements and; thus, future studies are need to assess its predictive accuracy early in the pregnancy course. These studies should take into account the potential confounders that were mentioned in our meta-analysis to limit heterogeneity.

Author contributions

Ioannis Bellos: performed the meta-analysis, conducted the electronic search and tabulated data, Georgia Fitrou: conducted the electronic search and tabulated data, Georgios Daskalakis: Wrote and revised the manuscript, Vasilios Pergialiotis: Conceived the idea, formed the tables, designed the statistical analysis and wrote the manuscript.

Conflicts of interest

None to declare

Funding

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.03.006.

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