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Enhancing the value of the sFlt-1/PlGF ratio for the prediction of preeclampsia: Cost analysis from the Belgian healthcare payers' perspective

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ABSTRACT

Objective: To evaluate the economic impact of introducing the soluble fms-like tyrosine kinase (sFlt-1) to placental growth factor (PlGF) ratio test into clinical practice in Belgium for the prediction of preeclampsia (PE).
Study design: We developed a one-year time-horizon decision tree model to evaluate the short-term costs associated with the introduction of the sFlt-1/PlGF test for guiding the management of women with suspected PE from the Belgian public healthcare payers' perspective. The model estimated the costs associated with the diagnosis and management of PE in pregnant women managed in either a test scenario, in which the sFlt-1/PlGF test is used in addition to current clinical practice, or a no test scenario, in which clinical decisions are based on current practice alone. Test characteristics were derived from PROGNOSIS, a non-interventional study in women presenting with clinical suspicion of PE. Unit costs were obtained from Belgian-specific sources. The main model outcome was the total cost per patient.
Results: Introduction of the sFlt-1/PlGF ratio test is expected to result in a cost saving of €712 per patient compared with the no test scenario. These savings are generated mainly due to a reduction in unnecessary hospitalizations.
Conclusions: The sFlt-1/PlGF test is projected to result in substantial cost savings for the Belgian public healthcare payers through reduction of unnecessary hospitalization of women with clinical suspicion of PE that ultimately do not develop the condition. The test also has the potential to ensure that women at high risk of developing PE are identified and appropriately managed.

1. Introduction

Preeclampsia (PE) is a major cause of maternal and fetal morbidity, long-term disability, and death worldwide, affecting 2–8% of all pregnancies and contributing to 10–15% of all maternal deaths [1–3]. PE is characterized by high blood pressure accompanied with either proteinuria, maternal organ dysfunction, and/or fetal growth restriction that arises, in most cases, after 20 weeks gestation [4]. In 2017, the incidence of PE in Belgium was 2.5% of all pregnancies (unpublished data from the Belgian Federal Public Service), which is similar to the approximate 2% incidence of PE in Europe [1,2]. However, the percentage of patients presenting with suspicion of PE can reach up to 10%

Abbreviations: BCFI, Belgian Center for Pharmacotherapeutic Information; DOS, days of stay; HELLP, Hemolysis, Elevated Liver enzymes, Low Platelet count; HIM, high intensity management; IIM, intermediate intensity management; LIM, low intensity management; LOS, length of stay; NICE, National Institute for Health and Care Excellence; NPV, negative predictive value; OWSA, one-way sensitivity analysis; PE, preeclampsia; PlGF, placental growth factor; PROGNOSIS, PRediction of short-term Outcome in preGNant wOmen with Suspected preeclampsIa Study; sFlt-1, soluble fms-like tyrosine kinase; SOC, standard of care.

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of the total pregnant population [5].

PE is a challenging disease to diagnose as it can be asymptomatic in the beginning, has a heterogenous presentation, and sometimes progresses rapidly [6,7]. Additionally, symptoms can be associated with other medical conditions [6]. Due to variations in the clinical presentations of PE, limited predictive accuracy of diagnosis remains, and therefore new methods to diagnose and manage this disorder are needed. The management of PE is also associated with significant healthcare costs [8,9]. In current practice, women already diagnosed with PE will be managed in an inpatient setting and those with suspected PE may also be hospitalized. However, as a result of the uncertainty in confirming diagnosis, those with suspected PE may be unnecessarily hospitalized, leading to further substantial healthcare costs [10]. Early and accurate diagnosis of PE is required, both to improve patient management and outcomes for the mother and fetus, as well as to reduce costs.

Circulating placental antiangiogenic and proangiogenic factors are altered in PE. Soluble fms-like tyrosine kinase-1 (sFlt-1) levels are increased and placental growth factor (PlGF) levels are decreased, resulting in a net antiangiogenic state that contributes to the onset of PE [11,12]. Quantification of the ratio between sFlt-1 and PlGF provides valuable diagnostic information and has formed the basis of the first automated diagnostic test for PE: the Elecsys® immunoassay sFlt-1/PlGF ratio on the cobas® electrochemiluminescence immunoassay platform (Roche Diagnostics GmbH, Mannheim, Germany) [13]. The analytical reliability and clinical value of this assay have been evidenced in a clinical study [14]. Additionally, measurement of the sFlt-1/PlGF ratio has been shown to be a better predictor of PE than either measure alone [15,16].

The PRediction of short-term Outcome in preGNant wOmen with Suspected preeclampsIa Study (PROGNOSIS) is an international, multicenter, prospective, double-blind, non-interventional study that validated cut-off values for the use of the sFlt-1/PlGF ratio in the short-term (up to four weeks) prediction of PE [10,17]. The study found that in 1050 pregnant women with suspected PE, between 24 + 0 weeks and 36 + 6 weeks gestation, a sFlt-1/PlGF ratio of $\leq$ 38 accurately ruled out the occurrence of PE within one week, with a negative predictive value (NPV) of 99.3% [10,17]. A ratio of $>$ 38 indicated an increased risk of developing PE within four weeks, with a positive predictive value of 36.7% [17]. From these studies, the ratio test appears to have met the European Union recommendation on value-based healthcare, which is achievement of the best outcomes with the available resources [18]. Furthermore, the health economic impact of the test, based on the PROGNOSIS data, has been assessed in a number of countries, with all analyses concluding that introduction of the ratio test into clinical practice is expected to result in cost savings compared with standard of care (SOC) without the test [19–24].

The objective of this study was to evaluate the economic impact of introducing the sFlt-1/PlGF ratio test into clinical practice versus the current SOC to aid in the diagnosis of PE in Belgium.

2. Methods

2.1. Model structure

An economic decision tree model for a one-year time horizon was developed in Microsoft Excel 2016 from a Belgian public healthcare payers' perspective, to estimate costs to the healthcare system (hospital inpatient and outpatient care) associated with the diagnosis, monitoring, and management of pregnant women presenting with clinical suspicion of PE, but in the absence of a definitive diagnosis. Expected management costs were compared between the SOC (no test scenario) and the SOC plus the sFlt-1/PIGF ratio (test scenario). The incidence of PE was assumed to be unaffected by the introduction of the test.

The model used data from the PROGNOSIS study [10,17], and simulated the movement of patients from the first suspicion of PE to hospital discharge following the birth. The PROGNOSIS study also provided information on inpatient length of stay (LOS), outpatient follow-up days, and days of treatment (DOT) [10,17]. Furthermore, the model shows the decisions about the management of the patient based on a clinician's assessment of the risk of developing PE, and the outcomes in terms of whether the woman actually develops PE; the model decision trees for the no test and test scenarios are shown in Fig. 1. Based on the outcomes of the assessment, patients entered either low intensity management (LIM), intermediate intensity management (IIM), or high intensity management (HIM). These categories were based on those from the UK model [19] and validated by Belgian experts. Patients that entered the HIM level were hospitalized and therefore managed in an inpatient setting, and those that entered the LIM or IIM levels were managed in an outpatient setting. The breakdown of resources used in the different categories are provided in Table S1.

As the sample size of the Belgian patients from the PROGNOSIS trial was small (n=108), the model uses the global PROGNOSIS data (n=1050). Nevertheless, the Belgian and global PROGNOSIS management decisions for women with suspected PE in the no test and test scenarios can be found in Table S2. As PROGNOSIS was a double-blind study, decisions regarding the management of patients were made without knowledge of their sFlt-1/PlGF status [10,17].

In the no test scenario, 36.1% of patients were hospitalized (HIM level) [17,19] and the rest of the patients were managed in an outpatient setting, evenly split between LIM and IIM (Fig. 1A and Table S2A). All patients remained in the same management pathway until they gave birth or developed PE. For the test scenario, women were classified into one of three groups according to their sFlt-1/PlGF ratio result, determined by the Elecsys immunoassay performed on the cobas electrochemiluminescence platform: <38; 38–85 (110); or >85 (110) (Fig. 1B). The cut-off value of 85 is used for early-onset (<34 weeks) PE and 110 is used for late-onset ($\geq$34 weeks) PE [15]. The risk of PE and the probability of hospitalization are expected to be positively correlated with the ratio value [19] and the result directly influences the management level. The lower cut-off value of 38 rules out PE within one or two weeks, with a NPV of 99.3% or 97.9%, respectively, derived from PROGNOSIS [17,25]. The higher cut-off value of 85 (110) for the diagnosis of PE was derived from a multicenter case-control study [15]. According to a 2015 consensus statement, a ratio >85 (110) indicates that PE is highly likely and should be managed according to local guidelines [26]. Patients with a ratio >85 (110) or 38–85 (110) entered either the IIM or HIM levels, and those with a ratio <38 entered either the LIM, IIM, or HIM levels (Fig. 1B).

A ratio <38 denotes a low risk of PE and, in principle, no women in this group would need to be hospitalized; however in practice, there may be other reasons for hospitalization. The model is based on the assumption that a woman with a ratio value <38 and blood pressure higher than 160/110 mmHg will be hospitalized, as recommended by local expert opinions and in line with the National Institute for Health and Care Excellence (NICE) UK guidelines [27,28]. From the PROGNOSIS data, the UK study determined that 1.7% of women met both these criteria (Table S2B) [19].

The model includes an option for a retest two weeks after the initial test in some cases where the initial test was negative (ratio <38) and the patient was not hospitalized. A retest was performed if the patient did not develop PE in the two weeks following their initial test, but presented with at least one of the following criteria: symptoms related to PE including epigastric pain, severe edema, headache, oliguria, or visual disturbance; confirmed hypertension or proteinuria; one or more criteria for HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome; intrauterine growth restriction; or abnormal uterine perfusion. The percentage of patients eligible for retest was 58.85%, based on the overall population of the PROGNOSIS trial. Of those retested, 90.4% had a ratio <38, 8.2% had a ratio 38–85 (110), and 1.4% had a ratio >85 (110). Patients who did not receive a retest remained in their original management intensity until they gave birth or developed PE. The

Fig. 1. Decision trees. a) The no test scenario (standard of care) and b) the test scenario (standard of care plus the sFlt-1/PIGF ratio test). HELLP, Hemolysis, Elevated Liver enzymes and Low Platelet count; HIM, high intensity management; IIM, intermediate intensity management; LIM, low intensity management; PE, preeclampsia.

decision tree structure for patients who received a retest is identical to that of the initial test (Fig. 1B).

2.2. Population

The inclusion criteria for the target population of this health economic model were pregnant women presenting with clinical suspicion of preeclampsia or identified to be at risk of developing preeclampsia, but in the absence of a definitive diagnosis. Therefore, this consisted of pregnant women with new onset of elevated blood pressure, aggravation of pre-existing hypertension, new onset of proteinuria, aggravation of pre-existing proteinuria, preeclampsia-related symptoms

(epigastric pain, excessive edema, severe swelling, headache, visual disturbance, or sudden weight gain), and/or preeclampsia-related findings (e.g. abnormal uterine Doppler sonography: mean pulsatility index >95th percentile in second trimester and/or bilateral uterine artery notching). The exclusion criteria were pregnant women with confirmed preeclampsia.

2.3. Costs

Consistent with Belgian Guidelines for Economic Evaluations and Budget Impact Analyses [29], the reference case analysis only included direct healthcare costs from the perspective of the healthcare payers, related to the diagnosis, monitoring, and management of women with clinical suspicions of PE and/or HELLP syndrome. The analysis included the cost of the sFlt-1/PlGF ratio test (€62.51 based on assumptions provided by Roche Diagnostics Belgium), treatment costs associated with hospitalization, outpatient appointments, anti-hypertensive medication, regular testing, and the cost of preventing complications. All costs were extracted from the National Institute for Health and Disability Insurance (RIZIV) codes, the Belgian Center for Pharmacotherapeutic Information (BCFI) database, and the Belgian Technical cell (APR-DRG 566) [30–32]. For all costs that were not calculated using the current prices, the appropriate Health Index figures were used to adjust for inflation [33]. The unit costs are displayed in Table S3. Management costs were calculated by multiplying the percentage of patients entering each management level by the daily treatment cost and the LOS for hospitalized patients or DOT for outpatients. The cost of treating complications included the cost of emergency admission to hospital (Table S3); the probability of emergency admission to hospital in the LIM and IIM levels was estimated to be 18%, which was derived from the PROGNOSIS data.

2.4. Cost–benefit analyses

A cost–benefit analysis quantified the financial burden of managing suspected PE and/or HELLP syndrome in Belgium. The expected costs of the no test scenario were compared with the ratio test scenario and uncertainty was evaluated using a one-way sensitivity analysis (OWSA). Using our model, the OWSA was performed by varying each parameter mean value by ±20% and reporting the impact of this change on the outcome. The structural uncertainty was handled via different scenario analyses.

3. Results

3.1. Cost–benefit analyses

3.1.1. Base case analyses

The model shows that additional information provided by the test may result in more appropriate decisions related to the management of women with suspected PE when compared with the current diagnostic procedures alone. Without the test information, 36.1% of women were hospitalized before a diagnosis of PE, of whom 26.4% went on to develop PE. If the additional information from the test had been available, the proportion of women hospitalized could have been reduced to 19.8%, of whom 36.8% would have subsequently developed PE. The increase in the percentage of hospitalized women who went on to develop PE when using the ratio test highlights a reduction in false positives; SOC results in 26.57% false-positive outcomes, while use of the test reduces this to 12.54%. This reduction in hospitalization using the test is expected to generate a cost saving of €712 per patient presenting with signs and symptoms of PE, which means an 18% decrease in the total costs in the base case analysis (Table 1).

3.1.2. Scenario analyses

Scenario analyses were performed to test the robustness of the results by comparing the base case with the Belgian PROGNOSIS data. Cost savings using the Belgian PROGNOSIS data were €982, with total costs for the no test and test scenarios of €3773.11 and €2791.42 per patient, respectively.

3.1.3. Sensitivity analyses

The deterministic OWSA evaluated the effect of varying the input parameters (±20%) on the incremental cost estimate, with the top variables shown in a tornado diagram (Fig. 2). The tornado diagram crossing point is the deterministic result of a €712 cost saving per patient. This sensitivity analysis shows that the proportion of patients hospitalized using SOC is the main driver of this result. As can be seen in the diagram, increasing this parameter by 20% (light blue bar) has a positive effect on the study results, improving the cost saving to €1087 per patient. On the other hand, a 20% increase in other values such as the percentage of women with a positive ratio test (>85) would reduce the cost saving.

4. Discussion

There is increasing focus on improving the value of laboratory medicine driven by the restraints on healthcare budgets and concentration on patient-centered healthcare [34]. In 2015, the International Federation of Clinical Chemistry and Laboratory Medicine Task Force on the Impact of Laboratory Medicine on Clinical Management and

Table 1
Cost analysis for the no test scenario compared with the test scenario.

Treatment timeline	No test					Test				
	Patient breakdown (%)				Costs (€)	Patient breakdown (%)				Costs (€)
	Total	LIM	IIM	HIM		Total	LIM	IIM	HIM	
Initial appointment[1]	100				30	100				93
Pre-PE management	100	32	32	36	1568	100	37.4	46.8	15.8	1002
PE management	18.5	4.6	4.6	9.3	1063	13.2	1.35	5.65	6.20	779
Second pre-PE management[2]						86.8	32.8	40.4	13.6	591
Second PE management[2]						5.3	1.9	2.3	1.1	262
No PE management	81.5	27.35	27.35	26.8[3]	818	81.5	30.9	38.1	12.5[3]	40
Total costs (per patient)			3479					2767		
Difference in cost (no test - test) per patient					712					

HIM, high intensity management; IIM, intermediate intensity management; LIM, low intensity management; PE, preeclampsia.
[1] The cost of the initial appointment was assumed to be the cost of the appointment with the specialist as well as the cost of a protein/creatinine ratio test and a blood pressure measurement. For the test scenario, the cost of the ratio test was also included. [2]Relevant for test scenario only and the retested subgroups. [3]These patients have a short stay in hospital before being discharged and treated in a non-hospitalized setting.

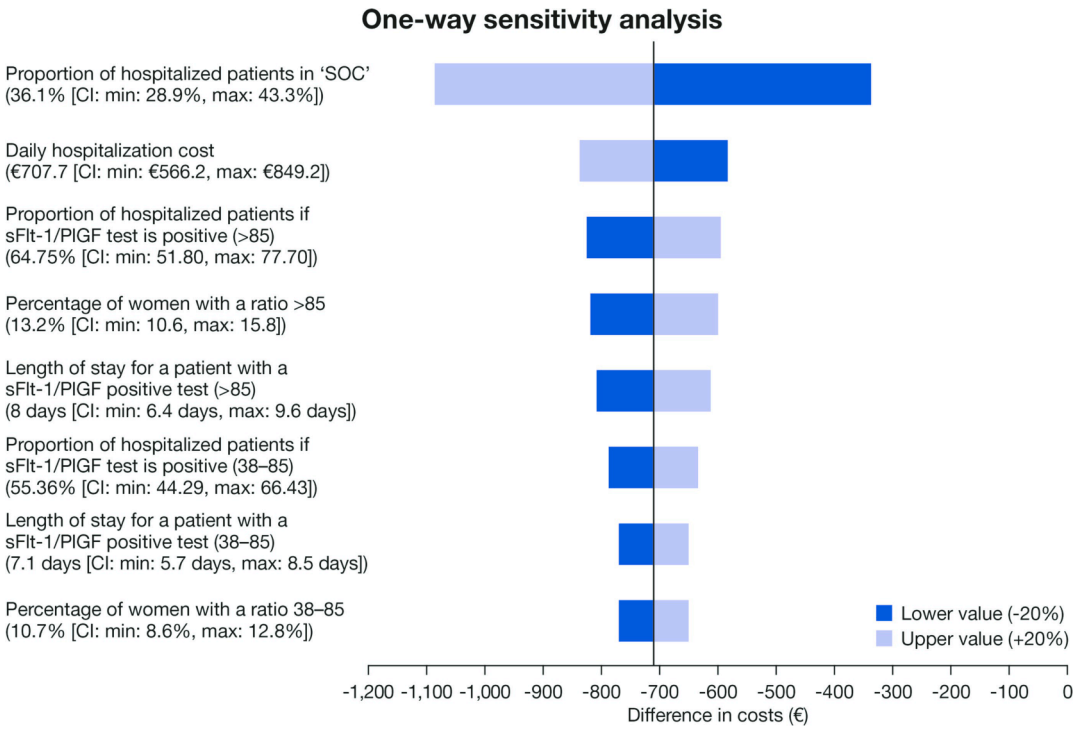

Fig. 2. One-way sensitivity analysis results. Each input parameter mean value was varied by ±20%, one at a time, and the impact of this change on the incremental cost estimate was reported. The parameters with the highest effect on the outcome are shown. The central axis represents the result of the base case analysis (€712 cost saving per patient). The light blue and dark blue bars represent the impact of the upper value (+20%) and the lower value (−20%), respectively, of each parameter. CI, confidence interval; SOC, standard of care; sFlt-1/PlGF, soluble fms-like tyrosine kinase/placental growth factor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Outcomes published a report identifying areas that could maximize the value of laboratory medicine, including improved utilization of new and existing biomarkers [35]. Previous studies of the sFlt-1/PlGF ratio test have proven its clinical efficacy in the prediction of PE [10,13,14,17] as well as its cost-effectiveness in various healthcare settings [19–24,28]. Our study adds further value to the ratio test, through highlighting the economic benefits of the introduction of the test in the Belgian healthcare setting versus current SOC without the test.

Our analysis of the PROGNOSIS data [17] revealed that almost half the number of patients were hospitalized and a cost saving of €712 per patient was expected when the ratio test was applied compared with SOC. According to the Belgian Statistical Office, in 2018 there were 117,800 deliveries in Belgium [36]. One in 10 pregnant women develop signs or symptoms related to PE [5], and therefore could benefit from the implementation of the ratio test. Based on those delivery figures and suspected PE cases [5,36], this represents an estimated yearly cost saving of €8.39 million for the Belgian healthcare payers with implementation of the test.

Scenario analyses revealed that the use of the ratio test produces higher cost savings for the Belgium PROGNOSIS data compared with the base case analyses. This is due to a higher hospitalization rate among patients with suspected PE in the no test scenario in Belgian hospitals compared with other countries. The difference in SOC in Belgium may be due to management and logistical reasons, including the availability of a one-step assessment process for inpatients. In the sensitivity analyses, the parameter with the highest impact on the cost outcomes was the proportion of patients hospitalized, which agrees with the finding that cost savings related to the test are directly linked to avoiding unnecessary hospitalizations for those with suspected PE.

Previous economic analyses in other countries, based on the PROGNOSIS data, also reported expected cost savings when applying the ratio test in clinical practice [19–24]. These cost savings varied across countries, likely due to differences in SOC procedures and variations in sample sizes within the global PROGNOSIS data. The expected cost saving results for Belgium were the highest of all the countries and most closely corresponded with those from Italy, which were €670 per patient [20]. Furthermore, other economic modelling studies performed in the UK, USA, and Germany have documented expected cost savings with introduction of the ratio test into clinical practice, with variations likely to be due to differences in the healthcare systems in the respective countries [37–40]. The influence of the ratio test on clinical decision-making in women with suspected PE has been investigated in Austria and Germany with the Preeclampsia Open Study (PreOS), where the test was found to influence routine clinical practice towards making appropriate hospitalization decisions [41,42].

The NICE model showed cost reductions of £2488 (~€3144) per patient compared with standard clinical assessment for the sFlt-1/PlGF ratio for women presenting with suspected PE between 20 and 34 + 6 weeks of gestation [28]. This resulted in NICE diagnostic guidance advocating the use of the ratio test as one of two recommended tests to help rule out PE within one week and avoid unnecessary hospital admissions [28].

A major strength of our study is that economic analysis was based on data from a large observational study [10], and is therefore likely to reflect real-world clinical practice. Another strength is the consistency with the NICE guidelines [28]. The main limitation of our study is the absence of a randomized controlled interventional study that shows the actual impact of the ratio test on ruling out PE within one week in clinical practice. The model uses a range of probable assumptions to simulate the effect of the most likely outcomes, however further research may be required to more accurately quantify the value of the test in routine practice. Another limitation, from the perspective of the Belgium healthcare system, is that the PROGNOSIS study includes data from other countries, whose clinical practice may differ, and the country-specific data for Belgium was from a relatively small cohort. Additionally, there are other commercially available tests to measure

PlGF and/or sFlt-1 [28], however conclusions from our study cannot be extrapolated to the use of other comparators. This is because the sFlt-1/PlGF cut-offs that are validated for the Elecsys immunoassays are not transferable to Kryptor immunoassays [43].

As discussed previously, the value of the ratio test has been proven in several healthcare systems and populations. However, this test should be complemented with an accurate combined first-trimester screening method and low-dose aspirin treatment in patients classified as high risk after assessment [44,45]. The health economic outcome of this screening method has been assessed in Belgium, which includes a cost-effectiveness analysis [46].

In conclusion, the introduction of the sFlt-1/PlGF ratio test in the Belgian healthcare setting will add value by impacting management decisions, improving the diagnosis procedure, and reducing the number of suspected PE hospitalizations, which translates into substantial cost savings for the Belgian public healthcare payers.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Details of ethics approval

As this was a health economic study, no ethical approval was required. However, in the PROGNOSIS study, each participating study site provided Ethics Committee/Institutional Review Board approval of the study protocol and associated documents before the start of the clinical part of the study. All women provided written informed consent before enrollment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2021.08.113.

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