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Extending the scope of pooled analyses of individual patient biomarker data from heterogeneous laboratory platforms and cohorts using merging algorithms

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Abbreviations: PlGF, placental growth factor; HDP, hypertensive disorders of pregnancy; BRC, best reference curve; IPD, individual patient data; GA, gestational age; MoM, Multiple of the Median; CI, confidence interval.

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ABSTRACT

Background: A common challenge in medicine, exemplified in the analysis of biomarker data, is that large studies are needed for sufficient statistical power. Often, this may only be achievable by aggregating multiple cohorts. However, different studies may use disparate platforms for laboratory analysis, which can hinder merging.
Methods: Using circulating placental growth factor (PlGF), a potential biomarker for hypertensive disorders of pregnancy (HDP) such as preeclampsia, as an example, we investigated how such issues can be overcome by inter-platform standardization and merging algorithms. We studied 16,462 pregnancies from 22 study cohorts. PlGF measurements (gestational age $\geqslant$20 weeks) analyzed on one of four platforms: R&D® Systems, Alere®Triage, Roche®Elecsys or Abbott®Architect, were available for 13,429 women. Two merging algorithms, using Z-Score and Multiple of Median transformations, were applied.
Results: Best reference curves (BRC), based on merged, transformed PlGF measurements in uncomplicated pregnancy across six gestational age groups, were estimated. Identification of HDP by these PlGF-BRCs was compared to that of platform-specific curves.
Conclusions: We demonstrate the feasibility of merging PlGF concentrations from different analytical platforms. Overall BRC identification of HDP performed at least as well as platform-specific curves. Our method can be extended to any set of biomarkers obtained from different laboratory platforms in any field. Merged biomarker data from multiple studies will improve statistical power and enlarge our understanding of the pathophysiology and management of medical syndromes.

1. Introduction

Large datasets are essential for sufficient statistical power to characterize subsets of disease. The usefulness of single cohorts can be enhanced by combining several studies to facilitate analyses of pooled individual patient data (IPD). However, to date such studies have only collected primary outcomes measured on comparable scales or, in the case of biomarkers, using the same assay platforms. Different assay platforms may vary in their sensitivity, precision, and concentration ranges. In such cases, valid methods of standardization of laboratory data are required in order to aggregate individual patient data.

The Global Pregnancy Collaboration (CoLAB) was established in 2011 (http://pre-empt.cfri.ca/colaboratory/global-pregnancy-collaboration) to facilitate data and sample sharing between research groups studying preeclampsia and other pregnancy disorders. Preeclampsia is a hypertensive disorder of pregnancy which complicates 3–4% of pregnancies and is a leading cause of maternal and fetal/neonatal mortality and morbidity worldwide. Because preeclampsia is clinically and biologically heterogeneous, (e.g. early and late disease have different prognoses and perhaps etiologies) improvements in management, prediction, diagnosis, prevention and treatment have been difficult to achieve [1–3].

Circulating maternal biomarkers of placental origin have been proposed as novel tools for identifying hypertensive disorders of pregnancy (HDP). However, to date, precise estimates of diagnostic sensitivity and specificity have yet to be achieved because individual studies have been too small. Clinical data can be easily standardized for aggregation of cohorts, but laboratory biomarker data present the unique problem that they often use different analytical platforms with different ranges and results.

This paper focuses on clinical and laboratory data for placenta protein, placental growth factor (PlGF) to predict and/or diagnose hypertensive disorders of pregnancy (HDP). These disorders are associated with severe reductions in circulating PlGF concentrations [1,4,5]. In the cohorts included in this study, PlGF was quantified on one of four laboratory platforms, each with different analytic performance. We developed a method of standardizing PlGF data to allow pooling. Additionally, concentrations of PlGF are known to change with gestational age (GA) and to show the power of the pooled data, we developed a best reference curve (BRC) over six gestational age groups. The rate of accurate identification of women with HDP using the merged BRC was compared to unmerged (platform-specific) rates.

This paper demonstrates a principle that can be generalized to the study of other biomarkers for any complex, heterogeneous medical conditions requiring large cohorts to draw useful conclusions, which also use different assay platforms to measure the same biomarker.

2. Materials and methods

2.1. Study database

In 2011–2012, we invited principal investigators with studies of circulating maternal angiogenic factors in pregnancy to participate in this study. We included any study in which maternal blood samples were collected at least once at any time during pregnancy (uncomplicated or otherwise) and had been analyzed for PlGF. Adequate clinical, demographic and pregnancy outcome information was necessary for inclusion. 22 cohorts were included in the present analyses (Supplementary material Table 1, with references to detailed information about each study, including individual patient consent and formal study research ethical approval). The datasets varied in sample size, maternal demographics as well as study design, including both low and high risk pregnancies. Missing data were retrieved, where possible. Individual datasets were integrated into one central database, which was cleaned and checked to ensure data integrity was maintained. Reported measures of PlGF below the limit of detection for each of the four platforms were recorded as the threshold value. These occurred in less than 1.5% of the observations and were not removed because these observations are expected to include the most severe cases of placental dysfunction associated with HDP.

The final database contained information on 16,462 pregnancies. Here we included only those women (n = 13,429) who had at least one PlGF measurement at or after 20 weeks' gestation (the time when preeclampsia presents clinically, by definition). Four different analytical platforms had been used by the included cohorts: Alere Triage PlGF, Roche Elecsys PlGF, R&D Systems PlGF and Beckman-Coulter PlGF. The number of pregnancies by cohort and analytical platform is listed in Supplementary material Table 1.