Augmented Intelligence for Clinical Discovery: Implementing Outlier Analysis to Accelerate Disease Knowledge and Therapeutic Advancements in Preeclampsia and Other Hypertensive Disorders of Pregnancy

Running Title

Augmented Intelligence for Clinical Discovery

Ghayath Janoudi

Thesis Supervisors

Dr. Mark Walker

Dr. Tammy Clifford

Thesis Advisory Committee

Dr. Angel Foster

Dr. Deshayne Fell

Dr. Joel Ray

Dr. Randy Giffen

Thesis submitted to the University of Ottawa in partial fulfillment of the requirements for the Doctorate in Philosophy degree in Epidemiology at the School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa

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BMI	body mass index
COVID-19	coronavirus disease of 2019
FACT	Folic Acid Clinical Trial
HELLP	hemolysis, elevated liver enzymes, and low platelet count
JBI	Joanna Briggs Institute
OaK	Ottawa and Kingston Birth Cohort
SD	standard deviation

THESIS PREFACE

Ethical Standards Disclosure

This study received Ottawa Hospital Research Institute (or OHRI) approval on March 01, 2022 (Certificate ID#: 3589) for secondary data analysis of the Folic Acid Clinical Trial (FACT) and the Ottawa and Kingston (OaK) Birth Cohort. The institutional approval included the research ethics approval by Ottawa Health Science Network Research Ethics Board (or OHSN-REB) for Protocol ID#: 20220109-01H.

Authors' Contributions

GJ contributed to the conception, design, acquisition of data, analysis, interpretation, drafting, and revision of the work. MW contributed to the conception, design, analysis, interpretation, and revision of the work. DF contributed to the conception, design, interpretation, and revision of the work. JR contributed to the conception, design, interpretation, and revision of the work. AF contributed to the conception, design, interpretation, and revision of the work. RG contributed to the conception, design, interpretation, and revision of the work. TC contributed to the conception, design, interpretation, and revision of the work. MU contributed to the acquisition of data, analysis, and revision of the work. SB contributed to the acquisition of data, analysis, and revision of the work. MR contributed to the acquisition of the data and revision of the work. GS contributed to the acquisition of the data and revision of the work.

THESIS ABSTRACT

Clinical observations of individual patients are the cornerstones for furthering our understanding of the human body, diseases, and therapeutics. Traditionally, clinical observations were communicated through publishing case reports and case series. The effort of identifying and investigating unusual clinical observations has always rested on the shoulders of busy clinicians. To date, there has been little effort dedicated to increasing the efficiency of identifying unique and uncommon patient observations that may lead to valuable discoveries. In this thesis, we propose and implement an augmented intelligence framework to identify potential novel clinical observations by combining machine analytics through outlier analysis with the judgment of subject-matter experts.

Preeclampsia is a significant cause of maternal and perinatal mortality and morbidity, and advances in its management have been slow. Considering the complex etiological nature of preeclampsia, clinical observations are essential in advancing our understanding of the disease and therapeutic approaches. Thus, the objectives and studies in this thesis aim to answer the hypothesis that using outlier analysis in preeclampsia-related medical data would lead to identifying previously uninvestigated clinical cases with new clinical insight.

This thesis combines three articles published or submitted for publication in peer-reviewed journals. The first article (published) is a systematic review examining the extent to which case reports and case series in preeclampsia have contributed new knowledge or discoveries. We report that under one-third of the identified case reports and case series presented new knowledge. In our second article (submitted for publication), we provide an overview of outlier analysis and introduce the framework of augmented intelligence using our proposed extreme misclassification contextual outlier analysis approach. Furthermore, we conduct a systematic review of obstetrics-related research that used outlier analysis to answer scientific questions. Our systematic review findings indicate that such use is in its infancy. In our third article (published), we implement the proposed augmented intelligence framework using two different outlier analysis methods on two independent datasets from separate studies in preeclampsia and hypertensive disorders of pregnancy. We identify several clinical observations as potential novelties, thus supporting the feasibility and applicability of outlier analysis to accelerate clinical discovery.

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I want to acknowledge the contributions of my co-authors, who have been instrumental in the success of this research. The process of publishing scientific research is often a collaborative effort and the co-authors I have worked with have demonstrated exceptional professionalism, attention to detail, and a willingness to work toward the best outcome for the project. I am grateful for the opportunity to work with them; their contributions have enriched the quality of this research.

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1 CHAPTER 1: INTRODUCTION

1.1 Clinical Discovery

Practising clinicians and healthcare professionals frequently face scenarios in which a patient's clinical presentation is unlike anything they have seen before. They can encounter situations in which the differential diagnosis is murky at best. And they can also find themselves in circumstances whereby a patient's clinical course improves or deteriorates unexpectedly. A common theme across these scenarios is that of a patient who defied the odds: the odds of presenting with a commonly seen set of symptoms and signs, the odds of experiencing a treatment effect in line with the published results, or the odds of progressing through the established natural history of the disease. While each patient's story is unique and valuable, the stories of patients defying the odds are incredibly captivating, inspirational, and motivational to the scientific and patient communities. In fact, such stories are frequently adapted and presented in many forms in popular literature, including TV shows like *Quincy, M.E.* and *House*, and acclaimed movies like Lorenzo's Oil. Perhaps the most intriguing aspect of these stories to the general public, and to clinicians in particular, is our inability to explain them, our insatiable curiosity to know how they came to be, and the allure of the possibility of uncovering hidden knowledge and discoveries that can help other patients.

Clinical observation and description of patients' presentation and progression are the sources of much of our medical knowledge of the human body, diseases, and therapeutics.[1-3] There is a long historical tradition of communicating medical knowledge, expertise, and advancement by describing clinical cases, their presentation, and management. Evidence of written clinical cases describing patient presentation and management can be found as early as 1600 BCE ― Before the Common Era ― in the Egyptian Edwin Smith Papyrus.[4] The Hippocratic Corpus contains numerous descriptions of clinical cases and patient encounters with Hippocrates (circa 460 BCE).[5] Claudius Galenus wrote extensively using clinical case reports (circa 216 Common Era).[6] And much of the written records (circa 929 Common Era) of Abū Bakr al-Rāzī are in the form of clinical case descriptions and presentations.[7]

Clinical case reports and case series continued to be essential sources of clinical discoveries and advancement in the modern era of medicine. Many important discoveries were first

communicated through case reports and case series. Some relevant examples include the description of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome in preeclampsia (1975),[8,9] the description of toxic shock syndrome and its association with tampon use (1978),[10,11] and descriptions of rare forms of infections and malignancy leading to the discovery of HIV infection (1981).[12,13] More recent examples include the description of pulmonary failure in patients vaping e-cigarettes (2018)[14] and the leading role clinical case reports and series played in the early phases of the coronavirus disease of 2019, or COVID-19, pandemic (2020).[15-19]

Despite their importance in advancing our understanding of diseases and therapeutics, the process of identifying and pursuing these unique clinical cases has mainly remained the same since antiquity. A keen and investigative healthcare professional will identify these unique clinical cases, then spend the time and energy to investigate and document them carefully.[1,20,21] However, this human-centric process of clinical discovery may not be efficient, especially considering the ubiquitous availability of medical data and the ever-increasing demands put on the shoulders of already busy healthcare professionals in the delivery of usual care.[22,23]

1.2 Outlier Analysis

The last two decades have witnessed considerable advancement in machine-learning technology, computer processing power, real-world data availability, and big data in the medical sphere.[24-26] These advancements present a valuable opportunity to streamline the process of detecting individual clinical cases with uncommon presentations or unexpected outcomes, allowing a systematic, reproducible, comprehensive, and real-time screening of large quantities of clinical cases. Such an approach would fuel the process of clinical discovery.

These aforementioned advancements have been applied in several related medical fields. A prime example is using statistical and machine-learning algorithms in drug discovery.[27-29] The main application of machine learning in drug discovery has been to identify highly promising chemical molecules from large chemical libraries, generate potential molecular structures based on desired properties, and model the pharmacokinetic properties of potential new drugs.[30-32] Another use of statistical and machine-learning algorithms in identifying single observations can be found in pharmacovigilance, aiming to detect safety signals.[33,34] The use of various data-

mining methods (a subset of machine learning) to detect potential safety signals has been proposed to shorten the time from market authorization to signal detection.[35]

Outlier analysis comprises a heterogenous set of statistical methods and machine-learning algorithms designed to identify observations that are significantly different from the majority of other observations.[36,37] D.M. Hawkins provides a commonly accepted definition of an anomalous or an outlier observation take from his *Identification of Outliers* published in 1980: "An outlier is an observation which deviates so much from the other observations as to arouse suspicions that it was generated by a different mechanism."[38] Traditionally, outliers are considered statistical noise in biostatistics and are often excluded from analyses.[39] However, distinguishing between statistical noise and true outliers, and understanding the mechanisms giving rise to the outliers, may lead to meaningful and valuable information. Such approaches can be seen in several established applications, including financial fraud detection, network connection anomalies, malware detection, and manufacturing quality control.[36,37]

Outlier analysis applications on medical data have been described for disease diagnosis, data quality assurance, screening for medication errors, and patient vitals monitoring and alerting.[40-43] The potential applications of these techniques on real-world data are broad and include discovering new clinical knowledge regarding the underlying disease process or preventive or therapeutic approaches that may be buried in the data.[44,45] This application can be critical in the obstetrics and pediatric fields, where patients have been traditionally excluded from the planning and conduct of pharmaceutical research.[46-48]

1.3 Augmented Intelligence

Identifying clinical cases that are unusual and unique is possible to achieve through outlier analysis. However, determining potential causes that gave rise to these outliers and uncovering these causes still need to be investigated by a subject-matter expert (i.e., a human being). This framework of machine analytics providing insight and information to be further consumed by a human actor for decision-making is known as a "symbiotic autonomous system," also commonly referred to as "augmented intelligence."[49] This term may have gained popularity in the past few years; however, much of a clinician's use of health technologies and diagnostics generally falls under this definition. As long as a computer system is not making a decision and a human is, then it falls under the framework of augmented intelligence.[49]

Augmented intelligence and artificial intelligence are two different concepts, although they are often used interchangeably.[49-51] As discussed in the previous paragraph, a critical difference between the two is that artificial intelligence is a technology that *simulates* human intelligence, while augmented intelligence is a technology that *enhances* human intelligence.[49,50] The general aim of artificial intelligence is the creation of systems that can perform tasks with either no or minimal human intervention. [49-51] Such is not the aim of augmented intelligence. Instead, augmented intelligence aims to enhance human intelligence by providing tools and techniques to assist human beings in making decisions and performing tasks. [49,52,53]

1.4 Preeclampsia

Advancing the rate of clinical discovery becomes ever more critical in fields traditionally neglected by commercial research. Obstetric diseases are a prime example of disease areas that chronically suffer from a lack of industry-sponsored research.[54] The dearth and paucity of drugs for obstetric diseases is a well-documented and recognized public health issue.[55,56] Obstetric diseases can therefore benefit greatly from increasing the efficiencies of the clinical discovery process.

Preeclampsia is a leading cause of maternal mortality and morbidity in obstetric diseases.[57,58] It is estimated that preeclampsia is responsible for 18% of all maternal deaths globally and affects 5% to 10% of all pregnancies.[59-62 63] Patients with preeclampsia can quickly deteriorate and develop life-threatening complications, including eclampsia and HELLP syndrome.[64-66] The only cure for preeclampsia is terminating the pregnancy, which often means an early and preterm delivery.[67] Preterm deliveries carry considerable immediate and long-term maternal and infant morbidity.[68,69]

Preeclampsia and its associated complications are some of the oldest ever recorded medical conditions; one of the first descriptions of eclampsia was recorded by Hippocrates in the 5th century BCE.[70] The temporal association between high blood pressure and proteinuria preceding eclampsia was described in several patients late in the 19th century.[71] Currently, preeclampsia is recognized as part of the wider spectrum of hypertensive disorders of pregnancy and is diagnosed when a new onset of proteinuria, maternal end-organ complication, or evidence of uteroplacental dysfunction coincides with gestational hypertension.[67]

Our understanding of the etiology of preeclampsia has advanced considerably since the first identification of hypertension and proteinuria as symptoms preceding eclampsia. Various pathophysiological mechanisms have been uncovered as playing a role in the disease. These include immune-mediated inflammatory processes,[72] imbalances in angiogenesis factors,[73] metabolic disorders,[74] and endothelial dysfunction.[75] In addition, there has been a greater understanding of the pivotal role of trophoblast invasion as directly related to the development of preeclampsia.[76-78] This understanding has led to the argument that preeclampsia is a two-stage disease: an abnormal placental development causing shallow trophoblast invasion and a latent maternal response to this abnormality.[76-78]

Despite these advances in understanding the pathophysiology involved in preeclampsia, there remain significant knowledge gaps in fully understanding the etiology.[79] Moreover, the management of preeclampsia has not changed much over the past two decades, with the possible exception of the recent addition of acetylsalicylic acid as a preventive measure against early preeclampsia in high-risk patients.[67] Beyond that, the recommended approach to managing patients with preeclampsia is close monitoring, controlling blood pressure, preventing seizures, and preparing for possible preterm delivery.[67,80-84] The armament of drugs available to a treating obstetrician is minimal.[67,80-84] There are four options for first-line antihypertensive therapy: methyldopa (introduced in the 1950s),[85] labetalol (introduced in 1977),[86] nifedipine (introduced in 1981),[86] and hydralazine (introduced in the 1950s).[80-84,87] Magnesium sulphate is the only option for preventing seizures. [80-84] Incidentally, magnesium sulphate was first used as prevention against preeclampsia in the early 1900s based on anecdotal descriptions of individual clinical cases.[88] Moreover, the use of methyldopa, labetalol, and nifedipine in pregnancy is listed under the “Warnings” or “Contraindications” sections in the Health Canada product monographs of these three drugs.[89-91]

Considering the high unmet need and the lack of industry-sponsored research, advancing the rate of clinical discovery in preeclampsia may bring about the discovery of repurposed medications, new risk factors, and an overall better understanding of the disease and patients’ journeys.

1.5 Objectives of the Studies

This thesis focuses on understanding the applicability of using outlier analysis to identify previously uninvestigated cases with the potential for clinical discovery. To that extent, we aim to address the following objectives.

1. To quantify the extent to which individual clinical case descriptions, through case reports and case series, have contributed to clinical discoveries in preeclampsia.
2. To synthesize the knowledge on the use of outlier analysis in the field of obstetrics research.
3. To introduce a framework of augmented intelligence using outlier analysis methods.
4. To apply the framework on data from the Folic Acid Clinical Trial (FACT) and the Ottawa and Kingston (OaK) Birth Cohort ― two datasets that assessed preeclampsia and hypertensive disorders of pregnancy.

1.6 Thesis Outline

This dissertation is an article-based thesis. It includes a total of three component articles: two are published and the third is a submitted manuscript. Chapter 2 is the first component article (published) and addresses objective 1 of the study, demonstrating the extent to which clinical case reports and case series have contributed to new discoveries in preeclampsia clinical research. Chapter 3 is the second component article (submitted manuscript) and addresses objectives 2 and 3, providing an overview of outlier analysis methods, demonstrating the extent of the use of outlier analysis in obstetrics research, and proposing a framework of augmented intelligence to be applied on medical data for accelerating clinical discoveries. Chapter 4, the third component article (published manuscript), addresses objective 4, demonstrating the framework's applicability to clinical trials and real-world data. Chapter 5 is a discussion and conclusion that connects the three papers into a cohesive argument and advocates for a dedicated effort to expand the research and institute organizational structures to implement the augmented intelligence framework on various medical data streams. Chapter 6 lists the references used in this thesis, except for the three individual papers, which cite their own reference lists. Chapter 7 lists appendices related to evidence of ethics review approval, publications, and submission.

2 CHAPTER 2: FIRST COMPONENT ARTICLE (PUBLISHED)

Do Case Reports and Case Series Generate Clinical Discoveries About Preeclampsia? A Systematic Review

2.1 Article Preface

The classical understanding is that unique and unusual clinical observations that can advance our understanding of diseases and therapeutics are first communicated through case reports and case series. There are undoubtedly many prominent examples in the literature of critical clinical discoveries first brought to light in case reports and case series. However, in our pursuit to understand clinical discoveries in preeclampsia, we wanted to quantify the proportion of unique clinical observations communicated through case reports and case series claiming to bring novel insight to the understanding and management of preeclampsia. We were unable to find such an analysis in the literature and therefore decided to investigate this evidence gap. This published article addresses the first objective of this thesis: 1. To quantify the extent to which individual clinical case descriptions, through case reports and case series, have contributed to clinical discoveries in preeclampsia.

GJ contributed to the conception, design, acquisition of data, analysis, interpretation, drafting, and revision of the work. MU contributed to the acquisition of data, analysis, and revision of the work. SB contributed to the acquisition of data, analysis, and revision of the work. DF contributed to the conception, design, interpretation, and revision of the work. JR contributed to the conception, design, interpretation, and revision of the work. AF contributed to the conception, design, interpretation, and revision of the work. RG contributed to the conception, design, interpretation, and revision of the work. TC contributed to the conception, design, interpretation, and revision of the work. MW contributed to the conception, design, analysis, interpretation, and revision of the work.

The article has been published in the *International Journal of Women's Health* and can be found here: Clinical discoveries about preeclampsia | IJWH (dovepress.com). The article can be cited as: Janoudi G, Uzun (Rada) M, Boyd ST, Fell DB, Ray JG, Foster AM, Giffen R, Clifford TJ, Walker MC. Do Case Reports and Case Series Generate Clinical Discoveries About

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2.2 Title

Do Case Reports and Case Series Generate Clinical Discoveries About Preeclampsia? A Systematic Review

2.3 Authorship

Ghayath Janoudi,[1,2] Mara Uzun (Rada),[3] Stephanie T Boyd,[1] Deshayne B Fell,[2,4] Joel G Ray,[5] Angel M Foster,[6] Randy Giffen[7], Tammy J Clifford,[2,8] Mark C Walker[1,2,9–12]

2.4 Author Affiliations

1 Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada
2 School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada
3 Independent Researcher, Ottawa, ON, Canada
4 Children's Hospital of Eastern Ontario (CHEO) Research Institute, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada
5 Departments of Medicine, Health Policy Management and Evaluation, and Obstetrics and Gynecology, St Michael's Hospital, University of Toronto, Toronto, ON, Canada
6 Faculty of Health Sciences, University of Ottawa, Ottawa, ON, Canada
7 IBM Canada, IBM, Toronto, ON, Canada
8 Canadian Institute of Health Research, Government of Canada, Ottawa, ON, Canada
9 International and Global Health Office, University of Ottawa, Ottawa, ON, Canada
10 Department of Obstetrics and Gynecology, University of Ottawa, Ottawa, ON, Canada
11 Department of Obstetrics, Gynecology & Newborn Care, The Ottawa Hospital, Ottawa, ON, Canada
12 BORN Ontario, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

2.5 Correspondence

Mark C Walker, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Centre for Practice Changing Research, Box 241, 501 Smyth Road, Ottawa, ON, K1H 8L6, Canada, Tel +1 613-798-5555 x76655, Email mwalker@toh.ca

2.6 Abstract

Background: Preeclampsia is a leading cause of maternal and perinatal mortality and morbidity. The management of preeclampsia has not changed much in more than two decades, and its etiology is still not fully understood. Case reports and case series have traditionally been used to communicate new knowledge about existing conditions. Whether this is true for preeclampsia is not known. Objective: To determine whether recent case reports or case series have generated new knowledge and clinical discoveries about preeclampsia.

Methods: A detailed search strategy was developed in consultation with a medical librarian. Two bibliographic databases were searched through Ovid: Embase and MEDLINE. We selected case reports or case series published between 2015 and 2020, comprising pregnant persons diagnosed with hypertensive disorders of pregnancy, including preeclampsia. Two reviewers independently screened all publications. One reviewer extracted data from included studies, while another conducted a quality check of extracted data. We developed a codebook to guide our data extraction and outcomes assessment. The quality of each report was determined based on Joanna Briggs Institute (JBI) critical appraisal checklist for case reports and case series.

Results: We included 104 case reports and three case series, together comprising 118 pregnancies. A severe presentation or complication of preeclampsia was reported in 81% of pregnancies, and 84% had a positive maternal outcome, free of death or persistent complications. Only 8% of the case reports were deemed to be of high quality, and 53.8% of moderate quality; none of the case series were of high quality. A total of 26 of the 107 publications (24.3%) included a novel clinical discovery as a central theme. Conclusion: Over two-thirds of recent case reports and case series about preeclampsia do not appear to present new knowledge or discoveries about preeclampsia, and most are of low quality.

Keywords: hypertensive disorders of pregnancy, eclampsia, HELLP syndrome, study design

2.7 Introduction

Knowledge of diseases, therapeutics, and the human body has been largely gained through the accumulation of clinical observations.[1–3] Meticulous observation is the cornerstone of clinical research, and scientific research in general.[2–5] Traditionally, case reports and case series have been utilized as a medium to communicate these preliminary clinical observations and discoveries.[6–8] These descriptive observational studies serve to generate scientific hypotheses that can then be tested further in comparative study designs.[9] Many medical discoveries have first been reported in the literature as case reports or case series. Several examples include lithium's and chlorpromazine's psychopharmacological properties,[10–12] malignant hyperthermia with dantrolene as its treatment,[13,14] toxic shock syndrome and its association with tampon use,[15,16] and the description of rare forms of infections and malignancies leading to the discovery of HIV infection.[17,18] Most recently, we have witnessed the use of individual clinical observations, communicated in various formats, in the detection and management of COVID-19.[19–23]

In antiquity, case reports were the main vehicles that physicians used to convey disease descriptions, treatments, and pass teachings.[24] The 20th century heralded large advancements in clinical study design and generated a strong debate on the role of case reports and case series. This culminated in the adoption of the evidence-based medicine hierarchy in the 1990s that relegated case reports and case series to the bottom of the clinical evidence pyramid.[7] Many peer-review journals no longer publish case reports. On the other hand, several journals have emerged that are specialized in publishing case reports and case series.[7,25] Despite being considered at the bottom of the clinical evidence hierarchy, case reports and case series are an integral part of evidence-based medicine practices.[26] This is why in 2014, a working group of researchers and methodologist was formed within The Joanna Briggs Institute (JBI), an international not-for-profit organization that aims to improve the quality of health care through evidence-based practices, to establish critical appraisal tools for case reports and case series.[27]

The hypertensive disorders of pregnancy are a leading cause of maternal mortality and morbidity worldwide,[28] and are responsible for approximately 18% of all maternal deaths globally and affect an estimated 5% to 10% of all pregnancies.[29–33] Preeclampsia is one such hypertensive disorder of pregnancy — a pregnancy complication characterized by resistant hypertension with

proteinuria or with other adverse conditions or complications.[34] Severe forms of preeclampsia can manifest as HELLP syndrome and untreated preeclampsia can lead to eclampsia.[35] Both HELLP and eclampsia are associated with a high degree of morbidity and mortality.[36–38] Hypertensive disorders of pregnancy and their associated complications are some of the oldest ever recorded medical conditions; one of the first descriptions of eclampsia was recorded by Hippocrates in the 5th century BCE.[39] Understanding of the pathophysiology of hypertensive disorders of pregnancy has grown since and has advanced considerably in the past two decades, yet the clinical management of preeclampsia has not changed much.[40–46] Similarly, preventive approaches to preeclampsia have mostly fallen short, with the exception of the use of Aspirin for the prevention of early severe preeclampsia.[47–49]

Considering the traditional role of case reports and case studies in medicine as a vehicle to communicate new clinical discoveries, we aimed to assess the extent to which recent case reports and case series have communicated clinical discoveries that have advanced our knowledge of preeclampsia through a systematic review. Systematic reviews in case reports and case series are common in the literature and traditionally aim to synthesize and assess rare clinical presentations or serious adverse events.[50–52]

2.8 Methods

We registered this study as a systematic review protocol on the international prospective register of systematic reviews (PROSPERO) under ID number CRD42020209953, with the outlined methods that follow. We added one amendment to the protocol to further clarify exclusion criteria and to define additional terms.

2.8.1 Search Strategy

We developed a detailed search strategy to identify case reports and case series on hypertensive disorders of pregnancy. The search strategy was developed in consultation with a medical information specialist (see Appendix S1) and consisted of controlled vocabulary, as well as keywords. The main search concepts were hypertensive disorders of pregnancy and case reports/case series. We searched two main bibliographic databases: Ovid Embase and Ovid MEDLINE. The search strategy filtered the results for human studies and the English language. Subsequently, we retrieved studies published between 2015 and 2020 for screening. We

conducted the search strategy on August 3, 2020, and did not conduct any additional searches or establish alerts.

2.8.2 Study Selection

This systematic review includes case reports or case series in pregnant persons diagnosed with hypertensive disorders of pregnancy. We outline the specific eligibility criteria in Table 1.

Table 1: Inclusion and Exclusion Criteria for the Systematic Review

	Inclusion Criteria	Exclusion Criteria
Population	Pregnant persons diagnosed with hypertensive disorders of pregnancy, including toxemia of pregnancy, preeclampsia, HELLP, and eclampsia	Patients who have not been determined to have hypertensive disorders of pregnancy, patients with secondary non–pregnancy-related hypertension, patients who were mistakenly diagnosed with hypertensive disorders of pregnancy but were determined to have another diagnosis, or a non-pregnant patient
Intervention/ Exposure	Any or none	No exclusion based on intervention/exposure
Comparators	Not applicable	Not applicable
Outcomes	Any or none	No exclusion based on intervention/exposure
Study Designs	Observational descriptive studies including case reports and case series	Comparative or experimental study design
Other	• English language • Published from 2015 to 2020 (inclusive) • Full text available	• Published 2014 or earlier • Published in a language other than English • Conference abstract • Commentary • Letters to the Editor

HELLP = hemolysis, elevated liver enzymes, and low platelet count.

Two independent reviewers screened all retrieved records in two stages: title and abstract screening (GJ and SB) and full-text screening (GJ and MU). We resolved rare disagreements through discussion; if we were unable to reach an agreement, we engaged a third independent reviewer (MW) as arbiter.

2.8.3 Data Extraction and Synthesis

The overall data extraction and synthesis process followed a content analysis approach. Upon completion of article selection, we used a random sample of 10 articles to develop a codebook to establish the required data extraction fields, as well as definitions of outcome categories. We used an additional random sample of 10 articles to further refine the codebook, as well as the data extraction sheet. After finalizing the codebook and extraction sheet, GJ performed all

extraction and abstraction activities. MU then conducted a data quality check on at least 20% of the extracted data.

For each included article, GJ extracted all data that were relevant to the study design characteristics, patients' baseline and demographic characteristics, intervention/exposure characteristics, and outcome characteristics.

Based on the information presented within the full text of each included article, GJ determined the severity of each patient's presentation or complication, the novelty of the exposure that the patient was reported to have experienced, whether the outcome was positive or negative, the reason for publishing the study, and whether a scientific hypothesis as a result of an observation was reported. We provide the definitions of these categories in Table 2.

We provided a descriptive summary of the number of case reports and case series within various categories and classifications. Additionally, we provided a narrative summary of case reports and case series that were determined to have a clinical discovery component. Data collected and used for this review, the codebook, and the extraction sheet are available from the corresponding author upon request.

Table 2: Outcome Categories, Category Classification, and Associated Definitions

Category	Classification	Definition
Case Presentation or Complication	Severe	A case in which the authors have explicitly used any of the following words: severe, life-threatening, poor prognosis, or similar severity-indicative language. In cases where there is no subjective qualifier from the authors, clinical judgment from the reviewer should determine the severity of the presentation.
	Moderate	A case in which the authors have explicitly used any of the following words: moderate, concerning, complicated, or similar language. In cases where there is no subjective qualifier from the authors, clinical judgment from the reviewer should determine the severity of the presentation.
	Mild	A case in which the authors have explicitly used any of the following words: mild, common, normal, or other similar language. In cases where there is no subjective qualifier from the authors, clinical judgment from the reviewer should determine the severity of the presentation.
	Unclear	Language used by the authors is insufficiently clear and ambiguous, and therefore there is insufficient information for the reviewer to make a determination.
Case Exposure	Novel	Authors describe a patient-related event prior to presentation with words that include novel, unusual, uncommon, unique, controversial, rare, or similar language in relation to the patient diagnosis. In a case where there is an exposure with no subjective qualifier, the reviewer — based on knowledge of the field — can judge whether a described event is uncommon and not previously reported in the type of presentation described in the study.

Category	Classification	Definition
	Common	Authors describe a patient-related event prior to presentation with words that include usual, standard, common, previously described, or similar language in relation to the patient diagnosis. In cases where there is an exposure with no subjective qualifier, the reviewer — based on knowledge of the field — can judge whether a described event is commonly associated and reported in the type of presentation described in the study.
	Unclear	Language used by the authors is insufficiently clear and ambiguous, and therefore there is insufficient information for the reviewer to make a determination.
	No exposure	The study does not describe a clear patient-related event prior to presentation that is explicitly described or is implied to have had an effect on the patient's disease presentation or progression.
Maternal Clinical Outcome	Positive	Authors describe the patient's outcome in a positive language. Examples include uneventful, well-tolerated, good, healthy, normal. If no language qualifier is available, the reviewer can make a determination of a positive outcome if the patient is alive with no long-term morbidity (more than 6 months) or other complications.
	Negative	Authors describe the patient's outcome in a negative language or a language indicative of death or long-term morbidity. Examples include passed away, severe adverse event, poor health, poor prognosis. If no language qualifier is available, the reviewer can make a determination of a negative outcome if the patient either died or developed long-term morbidity (more than 6 months) or other complications.
	Unclear	Language used by the authors is insufficiently clear and ambiguous, and therefore there is insufficient information for the reviewer to make a determination.
Publication Reason	Discovery	Authors describe their observations as new or reinforcing a relatively new hypothesis or concept, suggest changes to clinical management or further research into a well-defined observation, or do not provide references of similar observations and clinical findings despite clearly stating that an effort to do such was made. Discovery is further classified into presentation, exposure, management, outcome, or other. The three main publication classification reasons are mutually exclusive. However, subclassifications are not necessarily mutually exclusive.
	Education	Authors describe their publication as evidence-based, within a well-defined treatment paradigm, or based on a well-established disease description. In addition, authors provide advice or take-away clinical lessons as a central theme in their publication. Alternatively, authors clearly described their publication as educational material and have provided a clear educational discussion. Education is further classified into presentation, exposure, complication, management, or other. The three main publication classification reasons are mutually exclusive. However, subclassifications are not necessarily mutually exclusive.
	Other/unclear	Authors do not clearly identify their findings as either novel or educational, or the publication does not fall clearly in either the discovery or educational definitions. "Other" is further classified into presentation, exposure, complication, or management. The three main publication classification reasons are mutually exclusive. However, subclassifications are not necessarily mutually exclusive.
Scientific Hypothesis	Clearly stated	Authors provide a clear scientific hypothesis based on their clinical observations. Such a statement could describe a possible association between two patient-related events that is not directly supported or widely adopted in existing literature.

Category	Classification	Definition
	Implied	There is no clearly stated hypothesis in a paper that otherwise outlines a potential novel exposure, presentation, or treatment. The implied hypothesis can be potentially spread out in several sentences and is based on the reviewer assessment of case presentation, exposure, outcome, and publication reason.
	None	A paper that has been deemed as educational under the "publication reason" category.
	Unclear	There is insufficient information for the reviewer to make a determination.

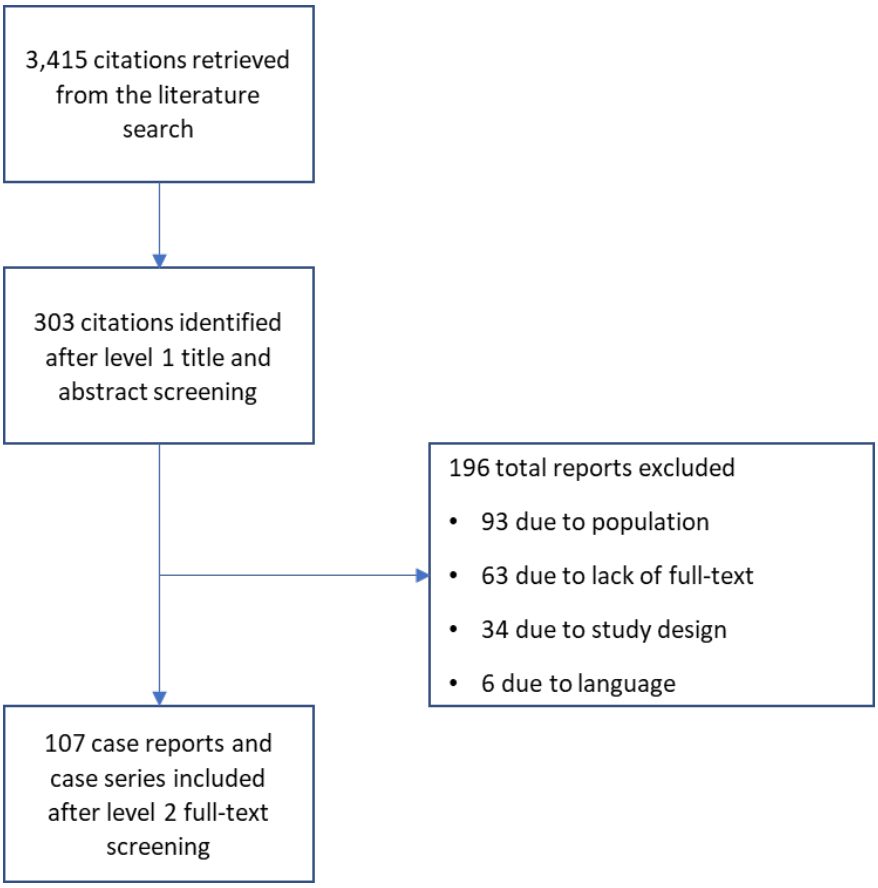
2.8.4 Quality Assessment

One reviewer (GJ) assessed the quality of the included case reports and case series according to the JBI critical appraisal Checklist for Case Reports and the JBI critical appraisal Checklist for Case Series.[53] The tool consists of eight questions for case reports and 10 questions for case series that are related to the existence or absence of various reported items. We deemed articles with reported items that addressed more than two-thirds of the JBI checklist to be high quality. More than one-third was deemed moderate quality, and less than one-third was deemed to be low quality.

2.9 Results

We retrieved a total of 3415 citations from the search strategy. After level 1 title and abstract screening, we selected 303 citations for level 2 full-text screening. After level 2 screening, we included 107 articles in this systematic review.[54–160] We provide a flow chart of included and excluded articles in Figure 1.

Figure 1: Flowchart of Included and Excluded Studies



Of the 107 included publications, three were case series[105,136,148] and the remainder were case reports. Authors reported on a total of 118 patients in these studies. Our quality assessment of the 104 case reports found that eight reports (8%) were high quality, 56 reports (54%) were moderate quality, and 40 reports (38%) were low quality. We found that the majority of the included case reports addressed two items on the JBI critical appraisal checklist for case reports: the description and presentation of a patient's history as a timeline (97% addressed this item), and the availability of take- away lessons (93% addressed this item). However, we found that only 17% of the included case reports provided sufficient description of a patient's demographic characteristics, which is the first item on the JBI checklist. Furthermore, only one-third of the included case reports provided sufficient description of the intervention (30%) and the post-intervention clinical condition (33%). A detailed description of the quality assessment of each included case report is available in Appendix S2.

We considered two of the three case series to be of low quality and one of moderate quality. All of the included case series described valid methods of identifying the condition of interest and two provided sufficient description on appropriate statistical methods used in the case series. A detailed description of the quality assessment of each included case report is available in Appendix S3.

In the included studies, maternal age and gestational age at first presentation were available for 115 patients, with a mean maternal age of 30.1 years (standard deviation [SD] = 6.6) and a mean gestational age of 29.7 weeks' gestation (SD = 6.5). Authors reported information on gravidity for 90 patients: 42 (47%) were primigravida. Authors included a clear presentation complaint for 108 patients; the most common reported symptom on presentation was abdominal pain (n = 33; 31%), followed by headaches (n = 26; 24%). On presentation, the mean systolic blood pressure reported in 92 patients was 163.1 mm Hg (SD = 27.5), while the mean diastolic blood pressure reported in 91 patients was 103.2 mm Hg (SD = 20.0). Authors only sporadically reported on other baseline characteristics, including body mass index, blood laboratory results, urinary laboratory results, liver function tests, and kidney function tests.

The most commonly reported hypertensive disorders of pregnancy diagnoses were preeclampsia (n = 98; 83%), HELLP (n = 40; 34%), hepatic hematoma — including rupture and infarction (n = 16; 14%), eclampsia (n = 10; 9%), and peripartum cardiomyopathy (n = 6; 5%). The most commonly reported interventions were magnesium sulphate (n = 46; 39%), labetalol (n = 15; 13%), hydralazine (n = 13; 11%), and nifedipine (n = 13; 11%). The authors reported that Caesarean section was the method of delivery for 61 patients (52%).

Based on how the authors reported the initial patient presentation in the case report or case series, we determined that a total of 96 patients (81%) had severe clinical presentations or complications during pregnancy, 15 patients (13%) had moderate clinical presentations or complications, and four patients (3%) had mild clinical presentations or complications. We determined there was insufficient information to categorize the severity of the presentations or complications in three patients (2.5%). We were unable to identify an environmental or pharmacological exposure that may have been associated with a patient's presentation in 105 patients (89%). Based on the description of patients' clinical outcomes in the included articles, we determined that maternal outcomes were positive in 99 patients (84%), negative in eight

patients (7%), and unclear in 11 patients (9%). These categories were defined a priori according to the Methods section and can be viewed in Table 2.

In assessing the publication reasons for the articles we studied, we determined that, of the 107 included articles, 65 (61%) were published as educational material and 26 (24%) as discovery articles; we were unable to determine a clear publication reason for 16 (15%) articles. We present a further breakdown of each classification in Table 3.

Table 3: Outline of the Results

Category	Classification	Result
Case Presentation or Complication	Severe	96 out of 118 patients (81%)
	Moderate	15 out of 118 patients (13%)
	Mild	4 out of 118 patients (3%)
	Unclear	3 out of 118 patients (3%)
Case Exposure	Novel	4 out of 118 patients (3%)
	Common	8 out of 118 patients (7%)
	Unclear	1 out of 118 patients (1%)
	No exposure	105 out of 118 patients (89.0%)
Maternal Clinical Outcome	Positive	99 out of 118 patients (84%)
	Negative	8 out of 118 patients (7%)
	Unclear	11 out of 118 patients (9%)
Publication Reason	Discovery: • presentation • exposure • management • outcome • other	26 out of 107 studies (24%):[a] • 5 studies • 5 studies • 13 studies • 2 studies • 9 studies
	Education: • presentation • exposure • complication • management • other	65 out of 107 studies (61%):[a] • 52 studies • 0 studies • 15 studies • 12 studies • 1 study
	Other/Unclear: • presentation • exposure • complication • management	16 out of 107 studies (15.0%):[a] • 10 studies • 2 studies • 4 studies • 4 studies
Scientific Hypothesis	Clearly stated	9 out of 107 studies (8%)
	Implied	22 out of 107 studies (21%)
	None	73 out of 107 studies (68%)
	Unclear	3 out of 107 studies (3%)

[a] There is an overlap in some of the studies.

Of the included studies with a clinical discovery aspect, the following interventions were considered notable ones in the assessment of the reviewers: sildenafil administration in a patient with periviable pregnancy and preeclampsia;[70] selective fetal reduction in cases of discordance in dichorionic twin gestations in patients with preeclampsia or HELLP syndrome;[87,92] continuous positive airway pressure in patients with obesity, obstructive sleep apnea, preeclampsia, and a high risk of developing severe preeclampsia;[107,159] acupuncture therapy in a patient with preeclampsia;[109] plasma exchange therapy for patients with HELLP syndrome;[121,132] eculizumab in a patient with HELLP syndrome;[117] eplerenone in a patient with obesity, obstructive sleep apnea, and preeclampsia;[129] pravastatin in a patient with HELLP syndrome;[137] and dydrogesterone to prevent preeclampsia in a patient with a history of recurrent preeclampsia.[150]

Authors of the included articles have clearly stated an observation-based scientific hypothesis in nine articles (8%), and we determined that there was an implied scientific hypothesis in 22 articles (21%). Based on our assessment criteria, we determined that the majority of articles (n = 73; 68%) did not include a clearly stated or implied scientific hypothesis. Finally, we were unable to make a determination in three cases (3%). We include a list of the studies that we determined to have reported a clear or implied hypothesis in Appendix S4.

2.10 Discussion

2.10.1 Main Findings

To our knowledge and best efforts, we were unable to find a previously published systematic review of case reports and case studies in patients with hypertensive disorders of pregnancy, including preeclampsia. Moreover, we were unable to find published peer-review articles that assessed the extent of clinical discovery contribution of case reports and case series in the field of preeclampsia. Over the period from 2015 to 2020, we identified a total of 104 case reports and three case series reporting on a total of 118 pregnant persons with a diagnosis related to hypertension disorders of pregnancy. Notably, we observed that there is tendency among the included articles to report on patients with severe presentation or complication (81%) and positive maternal outcomes (84%). Indeed, 96 of the 118 patients (81%) that were included in these articles had both a severe presentation or complication and a positive maternal outcome. Further, a sizable majority (61%) of identified manuscripts appeared to be published for

educational purposes rather than clinical discovery. We assessed that less than one-third of the included articles were published to communicate a potential clinical discovery (24%).

2.10.2 Interpretation

Case reports and case series can be an important part of the scientific discovery journey by communicating novel clinical observations in a structured and comprehensive manner. Our findings suggest that less than one-quarter of these studies in preeclampsia included a clinical discovery component. This begs the question of how today's novel clinical observations are being communicated with the larger scientific and clinical communities. Moreover, the tendency in reporting severe presentations and complications, coupled with positive maternal outcome, suggests that these case reports and case series are unlikely to be a representative sample of the population.

An important finding is the overall low adherence of the included case reports and case series to established reporting guidelines. Most pronounced was the lack of sufficient reporting on patients' characteristics, important measurements of the clinical condition (e.g., laboratory results), type of interventions, and post-intervention status. The lack of such information drastically reduces the educational and clinical discovery value of these articles. Ideally, authors should provide sufficient information on all aspects of the clinical encounter with the patients so as to allow clinicians and researchers to understand and potentially replicate or capture the population, intervention, and outcome in future studies. Authors should note any missing information relevant to the disease of which the case report is describing (e.g., blood pressure measurement in preeclampsia). Peer-review journals should ideally ensure that case reports and case series are as comprehensively reported as any other form of clinical study design, reporting on patients' characteristics so as to allow a full understanding of risk factors, potential environmental or pharmaceutical exposures, and all the results of relevant tests or examinations. We have outlined these deficiencies and provided recommendations to address them in Table 4.

Table 4: Identified Deficiencies in the Quality of Reporting of Case Reports and Case Series, and Corresponding Recommended Potential Solutions

Identified Deficiency	Recommended Solution
Reporting on patient demographic characteristics and current clinical condition	Include all relevant information that provides an understanding of a patient's risk factors at baseline. Authors should provide sufficient information so as to allow further research that may either utilize the presented data or attempt to identify patients with a similar clinical presentation and risk factors. Examples include race, income status, social supports, and initial vital signs.
Reporting on diagnostic test use, and the result(s) of those test(s)	Include the results of all diagnostic blood or imaging tests conducted and their normal ranges. Mention if a relevant or commonly performed diagnostic assessment was not done or could not be done (e.g., because of pregnancy, lactation, or because the patient was too unstable). Provide sufficient information so as to allow clinicians and researchers to interpret the value and the potential for use of diagnostic test(s) in future research.
Reporting on intervention(s) or treatment procedure(s)	Provide sufficient information on all interventions or treatment procedures that were performed to allow the replication or capture of such intervention(s) or treatment procedure(s) in future research.
Reporting on the clinical outcomes	Report clinically meaningful outcomes using standardized definitions or measures in a manner that can be replicated and captured in future research.
Identification of the intended purpose of the current publication	The reason for the current publication should be clearly stated in the abstract and the main text (i.e., what is the take-home learning point of the case report?). It should be clear as to whether the publication is intended to be an educational tool (e.g., how condition X is treated, or a review of the classic presentation of condition Y) or is to communicate a potentially novel clinical observation.
Formulation of a clear scientific hypothesis based on the case report or case series	Clarify that the observation is the initial stage of a potential scientific process. Communicate the reasons for why the condition (pathogenesis), the test (utility or modification), or the treatment (mechanism of action) may hypothetically work and what next steps could better test the hypothesis.

Case reports and case series have known methodological limitations, whereby they are unable to provide any type of valid statistical inference on the population for which the cases are being

described. These limitations have been amplified by misinterpreting the communicated clinical observations as a form of confirmatory evidence rather than exploratory findings that require further investigation.[161] This has led to the gradual loss of favour of case reports and case series, to the extent that certain journals no longer accept case reports for consideration.[162] As our findings suggest, case reports and case series are mostly used as a medium for educational purposes, with little regard to providing the same methodological rigour in comprehensive reporting that is expected from other study designs. This is further devaluing the clinical and scientific value of these important study designs.

As evident by the COVID-19 pandemic, there is an inherent need in the clinical and scientific communities to communicate unusual clinical observations or potentially beneficial forms of clinical management in a new disease area. While some communication of novel clinical observations in relation to COVID-19 have been conducted through the case reports and case series study design approaches, much has occurred in an unstructured manner through various internet-based communication platforms. This may suggest that there is room to rethink the traditional approach of identifying and communicating clinical discoveries.

2.10.3 Strength and Limitations

Through this systematic review, we comprehensively searched and screened all of the identified literature. In addition, we followed a content analysis approach where we developed a codebook to ensure standardization, consistency, and reliability of our data synthesis and assessment.

Limitations in this study include the restriction of the literature search to a five-year period, from 2015 to 2020. This limits the generalizability of our observation to the reviewed period. However, it is arguable that the assessment of the knowledge provided by case series and case reports over a five-year period is sufficient to demonstrate the overall value these methods of scientific communication have in the field of obstetrics. Another limitation is the restriction of our search strategy to the English language. This limits the generalizability of our findings to English-centred obstetrics clinical research. We also included three case reports that were communicated with the publishing journal in a “letter to the editor” format. This represents a minor protocol deviation, where we have excluded study types other than case reports and case series. We included these three case reports, as they were clearly describing clinical encounters with patients in an acceptable case report format.[129,140,142] Finally, only a fraction of the included

case reports was considered of high quality (7.7%) and none of the case series were of high quality. This reduced our ability to abstract all relevant data and to construct a meaningful picture of all the included articles, which resulted in some studies being classified as “other” or “unclear” in several categories.

2.11 Conclusion

In conclusion, our study suggests that the majority of case reports and case series related to hypertensive disorders of pregnancy do not offer new knowledge and are of poor quality. Only one-quarter of published case reports and case series published from 2015 through 2020 centred on a novel clinical observation or discovery and most of these focused on the management of preeclampsia. Lack of comprehensive reporting and an overall medium to low quality of the included studies limited the utility of these reports as viable sources of information for understanding and managing hypertensive disorders of pregnancy.

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2.13 Disclosure

The authors report no conflicts of interest in this work.

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2.15 Appendix S1 – Search Strategy

Ovid Embase Classic+Embase AND Ovid MEDLINE(R) ALL

1. Pregnancy.mp.

2. Pregnant Women.mp.

3. pregnan*.mp.

4. gestation.mp.

5. 1 or 2 or 3 or 4

6. Hypertension.mp.

7. high blood pressure.mp.

8. hypertens*.mp.

9. pre-eclamp*.mp.

10. preeclamp*.mp.

11. HELLP.mp.

12. 6 or 7 or 8 or 9 or 10 or 11

13. case stud*.mp.

14. case report.mp.

15. case series.mp.

16. 13 or 14 or 15

17. 5 and 12 and 16

18. (random* or sham or placebo*).mp.

19. ((singl* or doubl*) adj (blind* or dumm* or mask*)).mp.

20. (cohort adj stud*).mp.

21. (meta-analysis or systematic review).mp.

22. 18 or 19 or 20 or 21

23. 17 not 22

24. limit 23 to human

25. limit 24 to English

(The use of the asterisk in the search strategy is to instruct the search engine to search for the root word and retrieve all alternative endings.)

2.16 Appendix S2 – Quality Assessment of Included Case Reports

Author (and Year)	Were Patient's Demographic Characteristics Clearly Described?	Was the Patient's History Clearly Described and Presented as a Timeline?	Was the Current Clinical Condition of the Patient on Presentation Clearly Described?	Were Diagnostic Tests or Assessment Methods and the Results Clearly Described?	Was the Intervention(s) or Treatment Procedure(S) Clearly Described?	Was the Post-Intervention Clinical Condition Clearly Described?	Were Adverse Events (Harms) or Unanticipated Events Identified and Clearly Described?	Does the Case Report Provide Take-Away Lessons?	Final Quality Assessment
Abushoshah (2020)[46]	Yes	Yes	Yes	Yes	No	No	No	No	Moderate
Al Ghamdi (2018)[47]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	High
Altalbishi (2015)[48]	No	Yes	Yes	Yes	No	Yes	No	Yes	Moderate
Aoyagi (2015)[49]	No	Yes	No	Yes	No	Yes	No	Yes	Moderate
Araujo (2015)[50]	No	Yes	Yes	Yes	No	No	No	Yes	Moderate
Arcot (2015)[51]	No	Yes	No	Yes	No	No	No	Yes	Low
Aronsohn (2015)[52]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Artinger (2019)[53]	No	Yes	No	Yes	No	Yes	Yes	Yes	Moderate
Atuk (2018)[54]	No	Yes	No	Yes	No	No	No	Yes	Low
Balachandar (2019)[55]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Balci (2016)[56]	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Moderate
Belen (2015)[57]	No	Yes	No	No	Yes	No	No	Yes	Low
Berdai (2016)[58]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	High
Bijral (2018)[59]	No	Yes	No	Yes	No	No	Yes	Yes	Moderate
Booth (2018)[60]	No	Yes	Yes	Yes	Yes	No	No	Yes	Moderate

Author (and Year)	Were Patient's Demographic Characteristics Clearly Described?	Was the Patient's History Clearly Described and Presented as a Timeline?	Was the Current Clinical Condition of the Patient on Presentation Clearly Described?	Were Diagnostic Tests or Assessment Methods and the Results Clearly Described?	Was the Intervention(s) or Treatment Procedure(S) Clearly Described?	Was the Post-Intervention Clinical Condition Clearly Described?	Were Adverse Events (Harms) or Unanticipated Events Identified and Clearly Described?	Does the Case Report Provide Take-Away Lessons?	Final Quality Assessment
Bradke (2020)[61]	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Moderate
Brownfoot (2018)[62]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Cagan (2020)[63]	No	Yes	Yes	No	Yes	No	Yes	Yes	Moderate
Cao (2019)[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Celik (2015)[65]	No	Yes	No	Yes	No	No	No	Yes	Low
Chan (2018)[66]	No	Yes	No	Yes	No	No	No	Yes	Low
Chen (2016)[67]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	High
Chenkin (2016)[68]	Yes	Yes	Yes	Yes	No	No	No	Yes	Moderate
Chou (2016)[69]	No	Yes	No	Yes	No	Yes	Yes	No	Moderate
Dag (2015)[70]	No	Yes	No	Yes	Yes	No	No	Yes	Moderate
Davies (2020)[71]	No	Yes	No	No	No	Yes	No	Yes	Low
El-Agwany (2016)[72]	No	Yes	No	Yes	No	Yes	Yes	Yes	Moderate
El-Agwany (2016)[73]	No	Yes	Yes	Yes	No	Yes	No	Yes	Moderate
Escobar (2019)[74]	No	Yes	No	No	No	No	Yes	Yes	Low
Essa (2018)[75]	No	Yes	No	Yes	Yes	No	Yes	Yes	Moderate
Ferreira (2019)[76]	No	Yes	No	No	No	No	No	Yes	Low
Fervienza (2017)[77]	No	Yes	Yes	No	No	Yes	Yes	Yes	Moderate

Author (and Year)	Were Patient's Demographic Characteristics Clearly Described?	Was the Patient's History Clearly Described and Presented as a Timeline?	Was the Current Clinical Condition of the Patient on Presentation Clearly Described?	Were Diagnostic Tests or Assessment Methods and the Results Clearly Described?	Was the Intervention(s) or Treatment Procedure(S) Clearly Described?	Was the Post-Intervention Clinical Condition Clearly Described?	Were Adverse Events (Harms) or Unanticipated Events Identified and Clearly Described?	Does the Case Report Provide Take-Away Lessons?	Final Quality Assessment
Fotiou (2016)[78]	No	Yes	No	Yes	No	No	No	Yes	Low
Fuchs (2016)[79]	No	Yes	No	No	Yes	Yes	No	Yes	Moderate
Gainder (2015)[80]	No	Yes	Yes	No	No	Yes	Yes	No	Moderate
Ghazali (2019)[81]	No	No	Yes	No	No	Yes	Yes	Yes	Moderate
Ghorbanpour (2019)[82]	No	Yes	No	No	No	No	No	Yes	Low
Grimmett (2019)[83]	No	Yes	No	No	No	No	No	Yes	Low
Guerby (2020)[84]	No	Yes	No	No	No	Yes	No	Yes	Low
Guo (2018)[85]	Yes	Yes	Yes	Yes	No	No	No	No	Moderate
Hakata (2019)[86]	No	Yes	No	Yes	Yes	Yes	No	Yes	Moderate
Halliday (2017)[87]	No	Yes	No	No	No	No	No	No	Low
Hassan (2017)[88]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Moderate
Hauksdottir (2015)[89]	Yes	Yes	Yes	No	No	Yes	No	Yes	Moderate
Hayashi (2020)[90]	No	Yes	Yes	No	No	Yes	No	Yes	Moderate
Hinkson (2018)[91]	No	Yes	No	No	No	No	No	Yes	Low
Horazeck (2019)[92]	No	Yes	No	No	Yes	No	Yes	Yes	Moderate

Author (and Year)	Were Patient's Demographic Characteristics Clearly Described?	Was the Patient's History Clearly Described and Presented as a Timeline?	Was the Current Clinical Condition of the Patient on Presentation Clearly Described?	Were Diagnostic Tests or Assessment Methods and the Results Clearly Described?	Was the Intervention(s) or Treatment Procedure(S) Clearly Described?	Was the Post-Intervention Clinical Condition Clearly Described?	Were Adverse Events (Harms) or Unanticipated Events Identified and Clearly Described?	Does the Case Report Provide Take-Away Lessons?	Final Quality Assessment
Horie (2019)[93]	No	Yes	No	No	No	Yes	No	Yes	Low
Hussain (2019)[94]	Yes	Yes	Yes	No	No	No	No	Yes	Moderate
Jugnanden (2020)[95]	No	No	No	No	No	No	No	Yes	Low
Kaltofen (2019)[96]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Kasai (2016)[98]	No	Yes	No	No	No	No	Yes	Yes	Low
Kim (2020)[99]	No	Yes	No	Yes	Yes	No	No	Yes	Moderate
Kinay (2018)[100]	No	Yes	Yes	No	No	No	No	Yes	Low
Kocher (2019)[101]	No	Yes	No	Yes	Yes	Yes	No	Yes	Moderate
Koseoglu (2017)[102]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Kubota-Sjogren (2015)[103]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Kumarasinghe (2017)[104]	No	Yes	Yes	No	No	No	Yes	Yes	Moderate
Kuwabara (2020)[105]	No	Yes	No	No	No	No	No	Yes	Low
Lee (2017)[106]	No	Yes	No	Yes	No	Yes	Yes	No	Moderate
Lee (2017)[107]	No	Yes	No	No	No	Yes	Yes	Yes	Moderate
Loh (2017)[108]	No	Yes	No	No	Yes	Yes	No	Yes	Moderate
Lokki (2020)[109]	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Moderate

Author (and Year)	Were Patient's Demographic Characteristics Clearly Described?	Was the Patient's History Clearly Described and Presented as a Timeline?	Was the Current Clinical Condition of the Patient on Presentation Clearly Described?	Were Diagnostic Tests or Assessment Methods and the Results Clearly Described?	Was the Intervention(s) or Treatment Procedure(S) Clearly Described?	Was the Post-Intervention Clinical Condition Clearly Described?	Were Adverse Events (Harms) or Unanticipated Events Identified and Clearly Described?	Does the Case Report Provide Take-Away Lessons?	Final Quality Assessment
Luna Russo (2015)[110]	No	Yes	No	Yes	Yes	No	No	Yes	Moderate
Manning (2018)[111]	No	Yes	No	No	No	No	No	Yes	Low
Martingano (2018)[112]	No	Yes	No	Yes	No	No	No	Yes	Low
Martins (2017)[113]	Yes	Yes	Yes	No	No	No	Yes	Yes	Moderate
Mathias (2019)[114]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	High
Mikolajczyk (2017)[115]	No	Yes	No	No	No	No	No	Yes	Low
Millan (2017)[116]	No	Yes	Yes	No	No	No	No	Yes	Low
Mor (2015)[117]	No	Yes	Yes	No	No	No	No	Yes	Low
Morgan (2019)[118]	No	Yes	Yes	No	No	No	Yes	Yes	Moderate
Morisawa (2020)[119]	No	Yes	Yes	Yes	Yes	No	No	Yes	Moderate
Morisawa (2015)[120]	No	Yes	No	Yes	No	No	No	Yes	Low
Morton (2017)[121]	No	Yes	No	No	Yes	No	No	Yes	Low
Mould (2020)[122]	No	Yes	No	No	No	No	No	Yes	Low
Moura (2019)[123]	No	Yes	No	No	No	No	No	Yes	Low

Author (and Year)	Were Patient's Demographic Characteristics Clearly Described?	Was the Patient's History Clearly Described and Presented as a Timeline?	Was the Current Clinical Condition of the Patient on Presentation Clearly Described?	Were Diagnostic Tests or Assessment Methods and the Results Clearly Described?	Was the Intervention(s) or Treatment Procedure(S) Clearly Described?	Was the Post-Intervention Clinical Condition Clearly Described?	Were Adverse Events (Harms) or Unanticipated Events Identified and Clearly Described?	Does the Case Report Provide Take-Away Lessons?	Final Quality Assessment
Mousseaux (2020)[124]	No	Yes	No	No	Yes	No	Yes	Yes	Moderate
Nakakita (2015)[125]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	High
Narasimhulu (2015)[126]	No	Yes	No	No	No	Yes	No	Yes	Low
Okumura (2017)[127]	No	Yes	No	No	No	No	No	Yes	Low
Otten (2017)[129]	No	Yes	No	No	Yes	No	Yes	Yes	Moderate
Pacarada (2106)[130]	No	Yes	No	No	No	No	No	Yes	Low
Pritchard (2015)[131]	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Moderate
Quiros (2016)[132]	No	Yes	Yes	Yes	No	No	No	Yes	Moderate
Sarkissian (2018)[133]	No	Yes	Yes	No	No	Yes	Yes	Yes	Moderate
Senthilnathan (2017)[134]	No	Yes	No	No	Yes	No	No	Yes	Low
Shah (2018)[135]	No	Yes	No	No	No	No	No	Yes	Low
Sharma (2019)[136]	No	No	No	No	No	No	No	Yes	Low
Shirozu (2017)[137]	No	Yes	No	Yes	Yes	No	No	Yes	Moderate
Si (2017)[138]	No	Yes	No	No	Yes	No	Yes	Yes	Moderate
Sienas (2018)[139]	No	Yes	No	Yes	Yes	No	Yes	Yes	Moderate

Author (and Year)	Were Patient's Demographic Characteristics Clearly Described?	Was the Patient's History Clearly Described and Presented as a Timeline?	Was the Current Clinical Condition of the Patient on Presentation Clearly Described?	Were Diagnostic Tests or Assessment Methods and the Results Clearly Described?	Was the Intervention(s) or Treatment Procedure(S) Clearly Described?	Was the Post-Intervention Clinical Condition Clearly Described?	Were Adverse Events (Harms) or Unanticipated Events Identified and Clearly Described?	Does the Case Report Provide Take-Away Lessons?	Final Quality Assessment
Suzuki (2020)[141]	No	Yes	No	Yes	No	No	No	Yes	Low
Takahashi (2017)[142]	No	Yes	No	Yes	No	No	Yes	Yes	Moderate
Tanaka (2015)[143]	Yes	Yes	Yes	Yes	No	No	No	Yes	Moderate
Tolefac (2018)[144]	No	Yes	Yes	Yes	Yes	No	No	Yes	Moderate
Tolera (2018)[145]	No	Yes	Yes	No	No	No	No	Yes	Low
Tran (2020)[146]	No	Yes	No	Yes	No	No	No	Yes	Low
Tripathy (2018)[147]	No	Yes	No	No	No	No	No	No	Low
Troja (2015)[148]	No	Yes	No	No	No	No	No	Yes	Low
Tskhay (2016)[149]	No	Yes	No	Yes	No	Yes	Yes	Yes	Moderate
Vanden Eede (2018)[150]	No	Yes	Yes	Yes	Yes	No	No	Yes	Moderate
Whitehead (2015)[151]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Moderate
Zhang (2019)[152]	No	Yes	No	No	No	No	No	Yes	Low

2.17 Appendix S3 – Quality Assessment of Included Case Series

Author (Year)	Were There Clear Criteria for Inclusion in the Case Series?	Was the Condition Measured in a Standard, Reliable Way for all Participants Included in the Case Series?	Were Valid Methods Used for Identification of the Condition for All Participants Included in the Case? Series?	Did the Case Series Have Consecutive Inclusion of Participants?	Did the Case Series Have Complete Inclusion of Participants?	Was There Clear Reporting of the Demographics of the Participants in the Study?	Was There Clear Reporting of Clinical Information of the Participants?	Were the Outcomes or Follow-up Results of Cases Clearly Reported?	Was There Clear Reporting of the Presenting Site(S)/Clinic(S) Demographic Information?	Was Statistical Analysis Appropriate?	Final Quality Assessment
Kanonge (2018)[97]	No	No	Yes	No	No	No	No	Yes	No	No	Low
Oliveira (2017)[128]	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Moderate
Suryawan (2020)[140]	No	No	Yes	No	No	No	Yes	No	No	Yes	Low

2.18 Appendix S4 – Hypotheses of Included Studies

Study (Author and Year)	Interpreted Hypothesis
Aronsohn (2015)[52]	Surgical treatment of enlarged thyroid in high-risk parturient may decrease the risk of cardiac arrest.
Balci (2016)[56]	Incomplete separation of the placenta in cases of intrauterine death of one twin, in cases of a discordance in dichorionic twins gestation, may be associated with the return of preeclampsia after initial resolution.
Brownfoot (2018)[62]	Sildenafil administration in patients with periviable pregnancy and preeclampsia maybe associated with prolonged gestation and improved outcomes.
Chen (2016)[67]	Unidentified factors or triggers in the maternal serum at initial presentation of preeclampsia was responsible for producing “dangerous” or "toxic trophoblastic debris" leading to deterioration of the condition through endothelial activation.

Study (Author and Year)	Interpreted Hypothesis
Fotiou (2016)[78]	Elevated uric acid and potassium concentration, as well as cysteine to methionine ratio in amniotic fluid, may be associated with preeclampsia.
Fuchs (2016)[79]	Selective feticide in cases of a discordance in dichorionic twins gestation may help resolve HELLP syndrome.
Ghazali (2019)[81]	In patients with preeclampsia and nephrotic range proteinuria, hypoalbuminemia may be a contributing factor to hyponatremia and ascites.
Grimmett (2019)[83]	Preeclampsia may cause hyponatremia.
Guerby (2020)[84]	Selective feticide in cases of a discordance in dichorionic twins gestation in the third trimester may be associated with a decrease in the substances involved in the physiopathology of preeclampsia and may lead to better maternal outcomes.
Hauksdottir (2015)[89]	Licorice ingestions in patients with an 11beta-HSD2 genetic defect may be associated with early severe preeclampsia.
Hayashi (2020)[90]	Spontaneous intrauterine death of a twin in a discordance in dichorionic twins gestation during the third trimester may be associated with the resolution of preeclampsia.
Hinkson (2018)[91]	Hyponatremia may be associated with adverse outcomes in patients with preeclampsia.
Kim (2020)[99]	In patients with preeclampsia and obstructive sleep apnea, CPAP may help control blood pressure and prolong pregnancy.
Kocher (2019)[101]	Acupuncture therapy may be associated with positive outcomes in patients with preeclampsia.
Kuwabara (2020)[105]	Enhanced expression of sFlt-1 in the syncytiotrophoblast may be part of the etiology of preeclampsia in patients with placental mesenchymal dysplasia.
Lokki (2020)[109]	Eculizumab may be associated with positive outcomes in patients with HELLP syndrome.
Manning (2018)[111]	Chronic cannabis use with *H. pylori* colonization maybe a risk factor for the development of preeclampsia.
Martins (2017)[113]	Plasma exchange therapy may be associated with the prolongation of pregnancy in cases with suspected preeclampsia and HELLP syndrome.
Morisawa (2020)[119]	Hemodialysis is associated with a decreased value of angiogenic and anti-angiogenic markers as predictive markers for preeclampsia.

Study (Author and Year)	Interpreted Hypothesis
Morton (2017)[121]	Eplerenone 25 mg twice daily may be associated with beneficial blood pressure control on patients who are obese, have obstructive sleep apnea, and have preeclampsia with resistant hypertension.
Mould (2020)[122]	Temporal shear wave elastography and shear wave dispersion abnormalities are correlated with B-Mode ultrasound imaging and liver function biochemical markers in patients with HELLP syndrome.
Mousseaux (2020)[124]	Plasma exchange therapy may be associated with positive maternal outcomes in patients with HELLP and diminished levels of *ADAMTS13*.
Nakakita (2015)[125]	sFlt1 apheresis may be associated with positive maternal outcomes in patients with early-onset preeclampsia.
Narasimhulu (2015)[126]	Complete placental involution of spontaneous intrauterine death of a twin in a discordance in dichorionic twins gestation is required for the resolution of preeclampsia.
Oliveira (2017)[128]	The observed increase in the impedance to flow in the ophthalmic artery after the administration of MgSO4 in a patient with preeclampsia may explain the mechanism of action of MgSO4 in preventing eclamptic seizure attacks.
Otten (2017)[129]	Pravastatin may be associated with positive outcomes in patients with HELLP syndrome.
Quiros (2016)[132]	High sFlt-1/PlGF ratio may be a useful test to distinguish between non-HELLP thrombocytopenia and HELLP syndrome.
Si (2017)[138]	Massive GI hemorrhage and the associated inflammatory response may be associated with the development of HELLP syndrome.
Tran (2020)[146]	Echocardiographic findings in patients with preeclampsia and acute myocardial infarction associated with asymmetric left ventricular hypertrophy may be reversible after the resolution of preeclampsia.
Tskhay (2016)[149]	Dydrogesterone may prevent preeclampsia in patients with a high risk of developing preeclampsia.
Whitehead (2015)[151]	CPAP in a patient with obstructive sleep apnea and preeclampsia may enable pregnancy prolongation and improved neonatal outcomes.

CPAP = continuous positive airway pressure; GI = gastrointestinal; HELLP = hemolysis, elevated liver enzymes, and low platelet count; sFlt-1 = soluble fms-like tyrosine kinase-1; MgSO4 = magnesium sulphate; PIGF = placental growth factor.

3 CHAPTER 3: SECOND COMPONENT ARTICLE (SUBMITTED MANUSCRIPT)

Outlier Analysis for Accelerating Clinical Discovery: An Augmented Intelligence Framework and a Systematic Review

3.1 Article Preface

In Chapter 2, we reported and discussed the results of our systematic review on the extent to which clinical case reports and case series have contributed to advancing our understanding of the pathophysiology and management of preeclampsia. We discovered that only 24.3% of the case studies and case series claimed to communicate a novel clinical observation and more than 90% were of low to medium methodological quality. This finding reinforced the need for a different and more efficient approach to identifying unique clinical observations. In this submitted manuscript, we borrow from the fields of machine learning and biostatistics, and an understanding of the clinical discovery process, to propose a more efficient approach to identifying unique cases that may contribute new knowledge and discoveries. We also address a knowledge gap on how the methods proposed in this framework have already been implemented in obstetrics research. To that end, this manuscript addresses two of the thesis objectives: 2. To synthesize the knowledge on the use of outlier analysis in the field of obstetrics research; and 3. To introduce a framework of augmented intelligence using outlier analysis methods.

GJ contributed to the conception, design, acquisition of data, analysis, interpretation, drafting, and revision of the work. MU contributed to the acquisition of data, analysis, and revision of the work. DF contributed to the conception, design, interpretation, and revision of the work. JR contributed to the conception, design, interpretation, and revision of the work. AF contributed to the conception, design, interpretation, and revision of the work. RG contributed to the conception, design, interpretation, and revision of the work. TC contributed to the conception, design, interpretation, and revision of the work. MW contributed to the conception, design, analysis, interpretation, and revision of the work.

The manuscript has been submitted to *PLOS Digital Health*.

3.2 Title

Outlier Analysis for Accelerating Clinical Discovery: An Augmented Intelligence Framework and a Systematic Review

3.3 Authorship

Ghayath Janoudi,[1,2] Mara Uzun (Rada),[3] Deshayne B Fell,[2,4] Joel G Ray,[5] Angel M Foster,[6] Randy Giffen,[7] Tammy J Clifford,[2,8] Mark C Walker[1,2,9–12]

3.4 Author Affiliations

1 Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada
2 School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada
3 Independent Researcher, Ottawa, ON, Canada
4 Children's Hospital of Eastern Ontario (CHEO) Research Institute, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada
5 Departments of Medicine, Health Policy Management and Evaluation, and Obstetrics and Gynecology, St Michael's Hospital, University of Toronto, Toronto, ON, Canada
6 Faculty of Health Sciences, University of Ottawa, Ottawa, ON, Canada
7 IBM Canada, IBM, Toronto, ON, Canada
8 Canadian Institute of Health Research, Government of Canada, Ottawa, ON, Canada
9 International and Global Health Office, University of Ottawa, Ottawa, ON, Canada
10 Department of Obstetrics and Gynecology, University of Ottawa, Ottawa, ON, Canada
11 Department of Obstetrics, Gynecology & Newborn Care, The Ottawa Hospital, Ottawa, ON, Canada
12 BORN Ontario, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

3.5 Correspondence

Mark C Walker, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Centre for Practice Changing Research, Box 241, 501 Smyth Road, Ottawa, ON, K1H 8L6, Canada, Tel +1 613-798-5555 x76655, Email mwalker@toh.ca

3.6 Abstract

Clinical discoveries largely depend on dedicated clinicians and scientists to identify and pursue unique and unusual clinical encounters with patients and communicate these through case reports and case series. This process has remained essentially unchanged throughout the history of modern medicine. However, these traditional methods are inefficient, especially considering the modern-day availability of health-related data and the sophistication of computer processing. Outlier analysis has been used in various fields to uncover unique observations, including fraud detection in finance and quality control in manufacturing. We propose that clinical discovery can be formulated as an outlier problem within an augmented intelligence framework to be implemented on any health-related data. Such an augmented intelligence approach would accelerate the identification and pursuit of clinical discoveries, advancing our medical knowledge and uncovering new therapies and management approaches. We define clinical discoveries as contextual outliers measured through an information-based approach and with a novelty-based root cause. Our augmented intelligence framework has five steps: define a patient population with a desired clinical outcome, build a predictive model, identify outliers through appropriate measures, investigate outliers through domain content experts, and generate scientific hypotheses. Recognizing that the field of obstetrics can particularly benefit from this approach, as it is traditionally neglected in commercial research, we conducted a systematic review to explore how outlier analysis is implemented in obstetric research. We identified two obstetrics-related studies that assessed outliers at an aggregate level for purposes outside of clinical discovery. Our findings indicate that using outlier analysis in clinical research in obstetrics and clinical research, in general, requires further development.

3.7 Introduction

Throughout history, medical knowledge has been advanced through clinical observation[1-3] — the latter also serving as a catalyst for future research and scientific discovery.[2-5] Traditionally, novel clinical observations have been communicated through case reports and case series published in medical journals.[6-8] Examples include the discovery of Kawasaki disease,[9] the discovery of Hantavirus Pulmonary Syndrome,[10] the discovery of the association between statin therapy and rhabdomyolysis,[11] the discovery of disulfiram for managing alcoholism,[12] and the discovery of several treatments for psychiatric conditions.[13-15] Several widespread therapeutics have been discovered through accidental clinical observations; these include aspirin' anti-thrombotic

effects, beta-blockers anti-hypertensive effects, botulism toxin for wrinkle treatments, sildenafil for erectile dysfunction, and glucagon-like peptide-1 for weight loss.[16-21] A common theme across many such discoveries is reporting an observation that stood out against what would otherwise be expected.

Due to their methodological limitations, case reports and case series may have somewhat fallen out of favour in the past two decades.[22,23] Nevertheless, they continue to offer new insights, as was evident by their re-emergence during the COVID-19 pandemic.[24-28] A number of prominent COVID-19 case reports have led the COVID-19 scientific discourse and exploration.[29-31] The role of case reports and case series in communicating new observations, generating hypotheses, and acting as the first step in advancing clinical research remains deeply entrenched in the medical community.[32-34] Even so, unique and valuable clinical observations may remain unreported due to the many competing priorities placed on busy clinicians and the uncertainty of medical journals' publishable case reports.

Outlier analysis offers a more efficient and streamlined alternative for identifying unique or unusual clinical observations. Specifically, it can identify an unusual observation that does not adhere to an expected behaviour;[35,36] that is, an observation which differs substantially from other observations, leading to suspicions that it originated from a distinct mechanism.[37] In biostatistics, outliers are conventionally considered to be statistical noise and are, therefore, often excluded from analyses.[38] However, distinguishing between statistical noise and an informative outlier, and understanding the mechanisms giving rise to the latter, may expose important and valuable information. Such an approach is now used in fields outside of medicine, including the aforementioned financial fraud detection, network connection anomalies, malware detection, and quality control in manufacturing processes, also previously mentioned.[39-42] Within the field of medicine, outlier analysis has been recently reported for the purposes of disease diagnosis, data quality assurance, and medication error screening, as well as for monitoring a patient's vital signs and then alerting a caregiver when those physiological measures considerably deviate beyond the normal parameters.[39-42]

This paper provides a non-technical overview of outlier analysis and considers how clinical discovery may be framed as an outlier analysis problem. Next, a general framework of augmented intelligence is proposed, whereby outlier analysis methods are used to continuously

monitor health-related data for novel clinical observations (i.e., deviations), which can then be investigated by content-matter experts. Finally, given that pregnant patients are most excluded from the planning and conduct of pharmaceutical research,[43-45] the use of outliers as means of advancing discoveries in obstetrics can be particularly of value. As such a systematic review was completed to identify how outlier analysis has been used in obstetric research.

3.7.1 Definitions and Fundamentals of Outlier Analysis

3.7.1.1 Definition of Outlier

Healthcare professionals engage in outlier analysis on a daily basis as part of clinical practice. A healthcare professional engaged in diagnosing a patient looks for signs and symptoms not normally observed in healthy individuals. The existence of these signs and symptoms identifies a patient as an "outlier" when compared with the expected healthy presentation; the disease is the underlying mechanism that gave rise to the outlier observation. This intuitive, clinical-based understanding can be transferred from the individual patient-physician interaction to outlier analysis of multidimensional data.

The interest in identifying and addressing outlier observations in a set of data has been ingrained in the practice of statistics in the past century.[37] Conventionally, the aim of identifying outliers has been to eliminate such observations from the analysis (i.e., data cleaning).[37,46,47] With the significant growth in the fields of statistics and machine learning throughout the past three decades, applications of outlier analysis found their way outside the realm of data cleaning and new terms emerged that are now frequently used interchangeably. Specifically, the terms outlier, noise, anomaly, and novelty appear frequently in this literature. Of these, anomaly and noise are perhaps the most common terms used to refer to observations that do not align with an expected or predefined behaviour or characteristic.

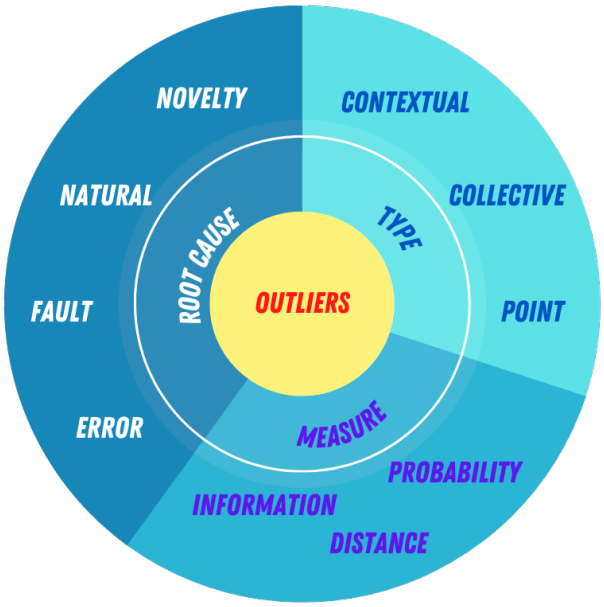
The most frequently used definition of outlier comes from the 1980 book *Identification of Outliers*, by D.M. Hawkins: "An outlier is an observation which deviates so much from the other observations as to arouse suspicions that it was generated by a different mechanism."[37] Similarly, an anomaly is frequently defined as an entity that does not conform to a defined notion of the normal.[46-48] In many instances, the terms outlier and anomaly are used interchangeably.[49] Attempts at differentiating various terms, one from another, are mostly related to the aim of the analysis and the degree to which the detected observation is found to be compelling or

interesting: anomalies are usually associated with observations that have real-life relevance,[50] novelties are associated with observations or patterns that have not been detected before,[51] and noise is associated with observations that clearly are due to random error and should be removed or accommodated.[52,53] We will be using the term outlier as an all-encompassing term that includes potential anomalies, novelties, and noise. A consistent element in the various published definitions of outliers is a predefined or expected normal behaviour, outcome, or model. In essence, an outlier is defined by its exclusion or deviation from what is understood as normal; and different outlier analysis methods are mostly distinguished by how that normal is defined and how the exclusion of non-normal observations is measured.

3.7.1.2 Characteristics of Outliers

We can characterize outliers by three attributes: root cause, type, and measure. The reader can find a graphic representation of these characteristics and their categories in Figure 2, followed by subsequent explanations of these attributes. We provide an outline of the characteristics, categories within these characteristics, and clinical examples for each category in Table 5 at the end of this section.

Figure 2: Characteristics and Categories of Outliers



Root Cause

Determining the cause that gave rise to the outlier observation is the ultimate goal of outlier analysis. This determination largely depends on domain knowledge, as well as knowledge of the method used to identify an outlier. Various root causes of outliers have been published in the literature.[35,54-59] These generally fall into four categories: error-based, fault-based, natural deviation, and novelty-based. Error-based outliers can arise from both human and instrument errors. Fault-based outliers are instances where the underlying system behaves in a manner that is indicative of a breakdown of an essential function or a malicious external activity; these can include disease states, fraudulent activities, or faulty equipment. Natural deviations include chance-based events, as well as those that can be explained by the underlying modelled process but lie to the extreme of the expected behaviour. Finally, and perhaps the most interesting, are the outliers that arise due to a generative mechanism that has not been accounted for in the expected behaviour or outcome. Such outliers may contain valuable information that can further our understanding and expectations of the issue at hand.

Type

Outliers are also distinguished by their type — the nature of the outlier in relation to its size and the surrounding context. We can classify outlier types into three categories: point outlier, collective outlier, and contextual outlier. [49,54,55,59,60] A point outlier is an individual observation (data point) that is determined to be an outlier from other observations; this is the most discussed type of outlier in the literature. For example, a patient diagnosed with a disease is a point outlier from the larger healthy population. The second category is the collective outlier, which refers to a group of data points that, by themselves, are not outliers but when put together are determined to be sufficiently different from the majority of other points. A clinically relevant example of a collective outlier is the detection of disease outbreaks, where, at a given time, a single case of a rare disease is not by itself an outlier from the expected behaviour of the disease, but a group of cases are an outlier. The final category is the contextual outlier; that is, outliers that are context-specific. A clinical example of a contextual outlier is a pregnancy-related physiological change and the associated signs and symptoms; should these signs and symptoms be reported outside the context of pregnancy, then it would give rise to a consideration of a disease state, which is an outlier to the expected healthy state of the majority of individuals.

Outlier Measure

A third important characteristic of an outlier is the type of measure that was used to determine its nature. A near-universal element in outlier analysis is when an unexpected outlier is measured against a predefined normal behaviour, outcome, or model. This type of measure can take several forms. The most common are distance-based measures, probability- and density-based measures, and information-based measures. [54,55,58,61-63] Distance-based measures identify outliers by judging how far they are from a predefined measure of a normal model or parameters. Most clinical laboratory testing uses this approach to highlight abnormal results. Another common clinical example is blood pressure, whereby if a measurement is a certain distance (in mm Hg) from an accepted upper limit (e.g., a systolic 120 mm Hg), then a patient is considered an outlier and is investigated further for hypertension. Probability-based measures, also referred to as density-based measures, identify outliers as an observation that is unlikely to exist in the manner in which it was identified. Unexpected outcomes that can occur during the course of treating a patient can be considered outliers under a probability-based measure. An example would be the progression of a bacterial upper respiratory infection to a case of pneumonia despite adequate anti-microbial treatment. Finally, information-based measures identify outliers by the effect their removal or addition has on our ability to form an accurate normal behaviour, outcome, or model that governs the rest of the data. A disease description with classic signs and symptoms is a good example of an information-based measure, whereby patients who present with signs and symptoms outside of a classic description can be classified as outliers. For example, a patient with preeclampsia presenting with loss of sight. The reason here is that if we are to incorporate "out-of-model" signs and symptoms, the disease description would be much more complex informationally and potentially less accurate to the majority of the observations. An information-based measure can also include what traditionally has been referred to as model-minimization or rule-based approaches.

Table 5: Clinical Examples of the Various Categories of Each Characteristic of Outlier

Characteristic	Category of Characteristic	Clinical Example
Root cause	Error	Entry of an additional digit in the weight field in a patient's electronic record.
	Fault	Congestive heart failure causing shortness of breath in a patient.
	Natural deviation	An exceedingly tall individual in height, with no underlying pathological process.

	Novelty	Exposure to a pharmaceutical compound for an unrelated indication, causing an unexpected alteration to the disease being studied.
Type	Point	A patient diagnosed with a disease is a point outlier relative to the larger healthy population.
	Collective	The cluster of a rare form of an infectious disease in a defined geographic area.
	Contextual	Physiological changes in pregnancy would be considered an outlier when compared to the general population but are otherwise normal when understood within the context of pregnancy.
Measure	Distance	The distance (degree) of the measured systolic blood pressure of a patient to an accepted upper limit determines if a patient meets the definition of hypertension.
	Probability	A rare adverse event that arises during the therapeutic management of a condition.
	Information	A suspected case of a disease that presents with a wide range of novel signs and symptoms not previously part of the traditional description of that suspected disease.

3.7.2 Approaching Outlier Analysis Methods

Inherent to the definition of an outlier is what we understand and define as normal or expected behaviour, outcome, or model from which the outlier deviates. A data model is a representation of this norm or expectation expressed in a manner that allows the objective assessment of outliers. The approach to structuring such a model will determine the method that the analyst needs to implement. The aim of this section is not to provide a comprehensive description of outlier detection methods, as such reviews can be found elsewhere. [54,58,61-67] Rather, we focus, instead, on providing a non-technical overview of outlier methods that can be applied to multidimensional data. Multidimensional data may include various data types (numeric, ordinal, and categorical) — such as patient records, as opposed to, for example, visual data (e.g., radiographs). Subsequently, we detail a generic process for determining the prerequisites that are essential for a valid outlier analysis.

3.7.2.1 Data Labels

Data labels refer to whether, in a given dataset, we know which observation is an outlier and which is a normal observation before we begin our analysis. [54,58,61-63] Outlier analysis is inherently a classification problem, where observations are classified as either outlier observations or normal observations. There are three scenarios that we can derive from data

labels. These three types of methods all share an implicit assumption that the normal observations far outnumber the outlier observations.[58]

Supervised Outlier Analysis Methods

This type of outlier analysis can take place when both normal and outlier observations are known — a situation that lends itself well to the use of supervised methods. Ideally, an analyst would develop a predictive model to distinguish between normal versus outlier observations and then apply the model to new observations to determine their class (normal observation or outlier observation). While supervised outlier analysis methods are likely to provide better results than semi-supervised and unsupervised methods, in practice, it is uncommon to come across a dataset that has both outlier and normal observations comparatively labelled. In addition, it is important to use approaches that can address the strong class imbalance, where outlier labels represent a small proportion of the dataset compared to the normal labels.[68] Supervised outlier analysis methods are identical to any regression or classification predictive models and follow the same approaches for feature selection and model tuning.

Semi-Supervised Outlier Analysis Methods

This is a scenario whereby only the normal observations are labelled. In such an approach, a data model is built that best represents the existing normal observations; new observations are assessed based on how well they can be explained by the developed data model.[54,58,61] Examples of semi-supervised models utilized for outlier analysis include kernel principle component analysis and one class support vector machine.[66]

Unsupervised Outlier Analysis Methods

Commonly, outlier analysis problems do not have a normal or an outlier label attached to the observation. In these cases, the analyst is forced to use unsupervised outlier analysis methods. Examples of unsupervised models utilized in outlier analysis are isolation forest and local outlier factor.[69,70]

3.7.2.2 Expected Characteristics of Outliers

Domain knowledge plays an essential part in guiding the approach to outlier analysis. Part of that is the prior determination of the desired characteristics of the outlier, as informed by the content-matter expert. Of the three outlier characteristics, two must be designated by the research team prior to conducting the analysis, to allow for the determination of the most appropriate method to

use. These two outlier characteristics are type (point outlier, collective outlier, and contextual outlier) and outlier measure (distance, probability, and information).

The largest body of literature on outlier analysis deals with the problem of point outliers.[58] These outlier analysis methods address the task of detecting single observations in a given dataset.[49] For a task that requires the detection of contextual or collective outliers, careful assessment of the method to be used must take place, as many point outlier methods will not be able to detect collective or contextual outliers.[64] Contextual and collective outliers may require reframing or redefining the task to allow for the utilization of point outliers methods.[49,64]

Determining the outlier measure is a function of both the domain knowledge and the nature of the available data. In the simplest form of a single-dimension (univariate) outlier analysis task, a domain expert should be able to speculate on how an outlier is usually determined through drawing from experience. However, once multidimensional aspects of the observation are introduced, the choice of an outlier measure can be highly dependent on the quality and characteristics of the dataset.[71,72]

3.7.2.3 General Model Assumptions

As is the case with any statistical analysis, any chosen outlier analysis method would have an inherent set of assumptions that, if not met, may lead to poor results. For example, in a common statistical model like linear regression, typical assumptions include linearity, normality, and independence. In the random forest model, assumptions include independence and feature stability. It's important to choose a model based on our ability to validate its assumptions.[35,55,56,71]

3.8 Clinical Discovery as an Outlier Analysis Problem

Classically, clinical discoveries were reported as a form of an unusual observation that stood out against that which was expected.[13-15] Considering the similarities of this classic approach to the definition of outliers, we propose to reframe the topic of clinical discovery into an outlier analysis problem. To that end, we suggest that clinical discovery is a contextual outlier, measured through an information-based approach and with a novelty-based root cause. Further, it is likely that this is a problem that falls under the unsupervised outlier analysis category. Following, we provide an argument in support of this reframing proposal to clinical discovery.

3.8.1 Novelty-Based

While the root cause determination of an outlier observation requires careful investigation by the analyst, as well as the content-matter expert, we can assume that in order for an outlier observation to contribute to clinical discovery, it needs to be generated through a mechanism that is not accounted for in the normal or expected behaviour, outcome, or model. While the discovery of an outlier observation due to other processes may be useful, such as the discovery of potential errors, the underlying generative process can still be accounted for by the normal expected behaviour had the error not taken place.

3.8.2 Contextual

A clinical discovery is a contextual outlier — it requires specific conditions for it to be detected as such and, in the absence of such conditions, the clinical discovery observation is likely to be missed. It is important to consider that the process of scientific discovery, in general, is not a random one. Discoveries require the investigators to actively guide their efforts to address the topics of interest. Similarly, an outlier analysis approach to clinical discovery needs to be defined within the context of the disease or clinical outcome of interest in order to yield relevant results. Conducting outlier analysis on patient data, without actively defining the context and conditions in which clinical discovery is sought, is unlikely to detect a valid clinical discovery.

3.8.3 Information-Based

While it is likely that both distance-based and probability-based outlier measures can be used in clinical discovery, we believe that an information-based measure best reflects the human-based approach to clinical discovery. An unusual clinical observation can be clinically described in a myriad of ways: through presentation, diagnostics, therapeutics, progression, or outcomes. However, one thing remains constant in all of these descriptions: the inability to reconcile the presentation with the learned model (i.e., the information summary) of the condition. It is thus likely that information-based measures have the potential to be most suitable for the task of outlier analysis in clinical discovery.

3.8.4 Unsupervised

Inherent to the task of clinical discovery is the lack of labelled observations that would otherwise reflect a case of clinical discovery. Thus, it is not possible to use supervised outlier analysis

approaches. In addition, labelling observations as normal, or non-discovery, requires significant investment and resource allocation, making it unlikely for us to use semi-supervised outlier analysis approaches. Unsupervised outlier analysis methods are therefore likely to be commonly used in the field of outlier analysis for clinical discovery.

3.9 An Augmented Intelligence Framework for Accelerating Clinical Discovery Through Outlier Analysis

Augmented intelligence refers to the implementation of machine learning and statistical learning models to enhance the capabilities, knowledge, and decision-making abilities of humans. Augmented intelligence adds a layer of information to the enhance human intelligence.[73]

Outliers are unusual and infrequent events. Indeed, the likelihood that an outlier is caused by a novel and previously unknown generative mechanism (i.e., a clinical discovery) is exceptionally rare. Thus, when starting an outlier analysis for clinical discovery, there is a need for awareness of the low probability of finding an outlier that might represent clinical discovery. However, even with an expected low probability of capturing a clinical discovery observation, outlier analysis will arguably detect more clinical discovery observations than the classic, human-based approach communicated through case reports and case series.

We propose the following approach to structuring outlier analysis projects for clinical discovery. The aim of the following steps is to maximize the potential of capturing novelty-based outliers and to maintain consistency across projects. An overview of these steps can subsequently be found in Figure 3.

3.9.1 Step 1: Define a patient population and a clinical outcome to be explored.

Outlier analysis for clinical discovery falls within the paradigm of exploratory research. While it is possible to conduct unsupervised outlier analysis on any dataset to determine outlier observations, without setting (i.e., grounding on) the clinical context, the outlier output is unlikely to be informative for clinical discovery. Setting the clinical context starts with formulating two clinical parameters: population and outcome of interest. Additional parameters are possible (e.g., some exposure or intervention) but may lead to a reduction of the available data for analysis. Considering the rare event rate of clinical discovery observations, a large dataset is always desirable. This approach is similar to the population, intervention, comparison,

and outcome (or "PICO") framework for generating clinical questions within the paradigm of evidence-based medicine.[74,75]

3.9.2 Step 2: Build a supervised predictive model of the chosen patient population and clinical outcome.

Various predictive modelling methods can be used to define the normal state and behaviour of the data in relation to the outcome. Predictive models provide a feasible, reproducible, and objective approach to the definition of normal or expected behaviour within the dataset in question. A predictive model should be built and optimized using the population and outcome defined in Step 1. In its essence, the aim of a predictive model is two-fold: to summarize and reduce the multidimensionality of the observations and to allow the detection of contextual outliers rather than point outliers. Reducing multidimensional data into a low-dimensional subspace is a common approach in outlier analysis and is based on the assumption that outliers are masked by the full dimensionality of the data.[71,76] Applying a predictive model that attempts to predict an outcome of interest within a relevant patient population will ensure our ability to detect outliers within the context that is of interest. Detecting contextual outliers is a common challenge in outlier analysis and one of the strategies to address this challenge is to reframe the analysis problem so as to only include the context of interest.[71]

3.9.3 Step 3: Determine the optimal measure to detect outliers.

Next, we must determine what type of measure to use and the threshold of that measure that can distinguish an outlier observation from a normal observation. Using a predictive model approach, two main tactics can be used: model fit measures and model outcome measures.

In a model fit approach, an outlier would be an observation that, if removed, would result in a model that can better predict the outcome. Depending on the predictive model used, there are a variety of model fit and model error measures that can be utilized. Torr and Murray (1993) utilize the iterative pruning of outliers and refitting of the model, aiming to minimize the least squares measure in a linear regression model.[77] In a similar fashion, John (1995) utilizes repeated pruning of decision-tree models until optimal tree representation is achieved. Nodes in the decision tree that were pruned out represent outliers and are systematically removed until a point where the majority of remaining points only represent normal points.[78] Also using a model fit

approach, Hawkins and colleagues (2002) and Williams and colleagues (2002) utilize a replicator neural network, whereby each data instance is reconstructed using a learned model and the reconstruction error is directly used as an outlier score for each instance reconstructed.[79,80] These are a few examples of established approaches of leveraging model fit to determine outliers.

In a model outcome approach, an investigator would use the prediction model output as a basis for determining outlier observation. One intuitive approach is to rank misclassified observations (i.e., observations that the model predicts wrongly) based on the confidence the model has assigned to the wrong prediction. An observation that was wrongly predicted with high confidence can be considered an outlier, as it has deviated substantially from the normal expected behaviour. This approach is analogous to how clinicians are likely to think of an unusual clinical encounter, whereby a certain expected clinical outcome (e.g., an improvement or deterioration of a condition) is not achieved despite high confidence that it should have materialized. However, using the model confidence score of wrong predictions requires the use of a predictive model that provides such label scores (e.g., regression models). A similar approach to outlier analysis can be seen in Roberts and Tarassenko (1994); the authors used expectation maximization to estimate a model distribution and then proceeded to estimate the probability that a given observation was at the extreme value of the distribution.[81] A model outcome approach is a form of an information-based outlier measurement, as the removal of the misclassified observation would improve the overall accuracy of the model. However, using the model outcomes to assess outliers allows us to incorporate any outlier measure approach. This is possible because using the outcomes of a predictive model has effectively turned the original multidimensional and general dataset into a single dimension problem. Moreover, the predictive model has reframed the original dataset into a proper context in relation to the prediction model outcome. We suggest using the information-based outlier measurement approach through identifying misclassification, together with the degree of the model confidence in the predicted classification. This approach would allow the investigator to use virtually any outlier analysis measurement approach, as the task has now been turned into an analysis of univariant data to detect point outliers.

The determination of both the outlier measure and the threshold for classifying outliers can be influenced by the predictive model diagnostic. Given a threshold, a model with higher accuracy will likely produce fewer outliers than a less accurate one. However, the proportion of outliers with novelty as a root cause is likely higher in more accurate models than in less accurate models.

3.9.4 Step 4: Content-matter experts to investigate an identified outlier observation for potential root causes.

The general aim of outlier analysis is to understand what caused an observation to deviate from the expected or normal behaviour, outcome, or model. Specifically, it aims to identify those observations that have deviated from the norm due to a unique underlying mechanism that can advance our clinical understanding of the area under investigation. Once an outlier observation has been identified in a given dataset, a panel of content-matter experts should review all details associated with the identified observation to understand why it deviated from the norm. The panel of content-matter experts can attribute an outlier observation to one of the four outlier root causes described earlier: error (e.g., a data entry error), fault (e.g., faulty instruments, fraud), natural deviation, or novelty (i.e., clinical discovery). The use of expert knowledge in various stages of outlier analysis, including verification of the correctness and studying of outliers, has been reported in several places across the outlier analysis literature.[82-84]

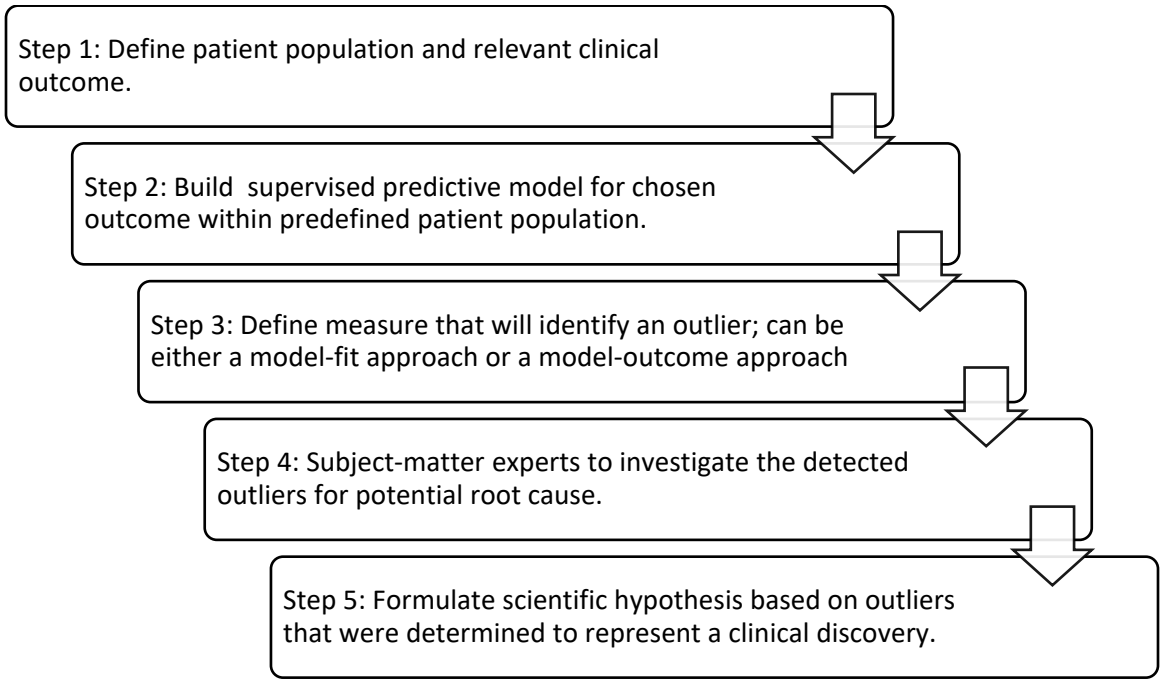
It is ideal that the panel of content-matter experts, once they identify a potential clinical discovery, seek additional information outside of what is captured in the existing data. The assumption here is that the underlying mechanism that gave rise to the outlier is not captured by the existing collected information in the dataset. Had such information been well-represented in the dataset, it is likely to have been accounted for in the predictive model.

3.9.5 Step 5: Use outliers determined as clinical discovery to formulate scientific hypotheses.

Outlier observations that have been concluded to represent a clinical discovery by the domain content-matter experts panel should be studied and a scientific hypothesis should be generated from these observations. It is important to note that the output of this framework is exploratory in nature and cannot provide any type of statistical inference, including causal inference. Any clinical insight gained from this framework must be further assessed in a proper comparative

study design. The aim of this augmented intelligence framework is to accelerate the rate of clinical discovery through the use of outlier analysis as opposed to relying on the classic approach to clinical discovery that is largely human-based. The increased efficiency will likely provide a greater rate of novel and promising insights.

Figure 3: Overview of the Augmented Intelligence Framework for Accelerating Clinical Discovery Through Outlier Analysis



3.10 Systematic Review of Outlier Analysis in Obstetric Research

Due to the challenges of conducting clinical trials with pregnant participants, obstetrics research is not supported by a strong industry that is incentivized to accelerate and commercialize discoveries. We are of the opinion that the field of obstetrics would benefit from applying outlier analysis to accelerate clinical discovery. To explore and assess the use of outlier analysis in obstetrics research, we conducted a systematic review.

3.10.1 Methods

3.10.1.1 Search Strategy

In consultation with a medical information specialist, we developed two search strategies covering three bibliographic databases. We provide the detailed search strategies in Appendix A.

We included controlled vocabulary, as well as keywords, with main search concepts related to obstetrics and outlier analysis methods. One search strategy was developed to search Embase and MEDLINE through the Ovid search engine. The second search strategy was developed to search Web of Science. We conducted the search on September 2, 2021.

3.10.1.2 Study Selection

We list studies that met our eligibility criteria in Table 6. Studies had to include a population of pregnant women and utilize an outlier analysis method that aimed to identify unusual observations rather than to remove statistical noise. We defined an outlier analysis method as any approach that has both of the two following elements:

- establishes or defines the normal or expected behaviour of the data or population being analyzed
- identifies specific observations or patterns in the data that do not conform to the established normal or expected behaviour.

These two criteria apply well to the definition of outliers discussed earlier and do not restrict the outlier approach to specific published statistical models and algorithms. These criteria would further allow the inclusion of non-quantitative approaches, such as a clinical decision rule-based approach to outlier analysis.

Table 6: Eligibility Criteria for the Systematic Review

	Eligibility Criteria
Population	Studies with a population that includes a pregnant person
Intervention/ Exposure	Any
Comparators	Not applicable
Outcomes	Any
Study Design	Any
Study Methods	The use of outlier analysis as part of the methods. Outlier analysis methods include any approach that: • establishes or defines a normal or expected behaviour, outcome, or model of the data or population being analyzed • identifies specific observations or patterns in the data that do not conform to the established norm or expectation

Other	• English language • Full text available

Two reviewers (GJ and MU) independently screened the title and abstract of the results retrieved from the search. Subsequently, we screened the full text of the eligible abstracts for the inclusion and exclusion criteria. We solved any disagreement between the two reviewers through discussion and if we were not able to reach an agreement, a third independent reviewer (MW) provided arbitration.

3.10.1.3 Data Extraction and Synthesis

One reviewer (GJ) extracted data relevant to the following categories: study characteristics, population characteristics, intervention/exposure, outcome measures, and outlier analysis method. Study characteristics included study design, publication year, setting, country of origin, inclusion and exclusion criteria, and sample size. Population characteristics included population selection criteria, baseline demographics, and other patient characteristics. Intervention/exposure included the type, characteristics, and duration of the intervention. Outcome measures included the definition and results. Outlier analysis included the type, features, approach to feature engineering, approach to data sampling for training-based models, model diagnostics and optimization, model performance results, and model validation.

To ensure accurate data extraction, a second reviewer (MU) conducted a check of the accuracy of 20% of the extracted data. As the aim of this systematic review was to explore and assess the use of outlier analysis methods, we did not conduct a quantitative meta-analysis for this systematic review. Instead, we planned an a priori narrative synthesis of the included studies.

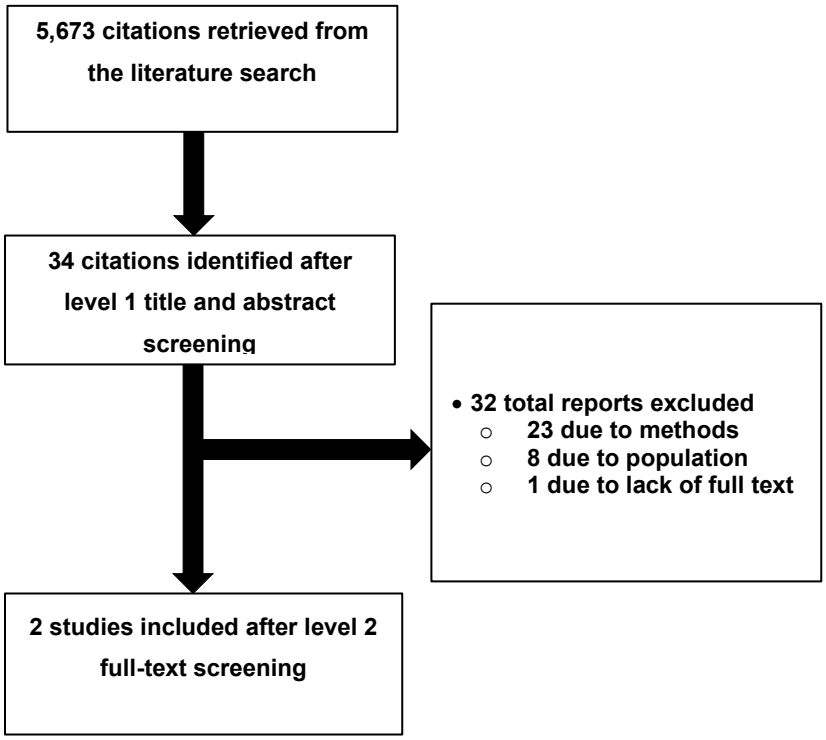
3.10.1.4 Quality Assessment

Currently, there is no standardized quality assessment tool for outlier analysis studies in clinical research. However, for those studies that included a predictive component, we used the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies: The CHARMS Checklist.77

3.10.2 Results

We retrieved 5,673 records after running our search. Subsequent to title and abstract screening, we selected 34 records for full-text screening. Of these, we further excluded 32 reports and found that two reports representing two unique studies met our inclusion and exclusion criteria.[86,87] A list of all excluded reports, together with the reason for exclusion, can be found in Appendix B. A PRISMA flow chart for included and excluded studies can be found in Figure 4.

Figure 4: PRISMA Flow Chart of Included and Excluded Studies



We did not assess the quality of either included study, as neither one had a predictive component.

In one of the included studies, Antonelli and colleagues proposed a framework for detecting clinical practice anomalies in health-related databases. The proposed framework consisted of determining patterns in medical records and comparing these patterns to published medical guidelines. Antonelli and colleagues (2013) applied the proposed framework to patient data from 905 pregnant persons. The authors analyzed the data for patterns in the frequencies in which the pregnant persons visited their healthcare providers for routine antenatal visits and contrasted these patterns with the medical guidelines from the Italian Ministry of Health (Ministerial Decree, 1998). Antonelli and colleagues did not describe a quantitative method for defining or

identifying anomalous patterns. Instead, the authors considered any antenatal visit pattern that did not adhere to the medical guidelines as an anomaly.[86]

The main two anomaly patterns reported by Antonelli and colleagues (2013) were the lack of fully utilizing the free examinations offered by the Italian Ministry of Health, and the higher frequency of examinations during the second and the third trimesters than recommended by the guidelines.[86] The second included study by Khan and colleagues (2017)[78] aimed, among other objectives, to identify spatial outliers of teenage birth rate in counties in the US. The authors utilized the National Vital Statistics System Birth Data files between 2003 and 2012 to provide a count of teen births at a county level. To identify counties with an outlier teen birth rate, the authors used Anselin Local Moran's I cluster and outlier analysis method to examine spatial outliers, with positive non-zero weights assigned to the eight closest neighbours to the target county. Spatial outliers were counties with a low or high teen birth rate, surrounded by counties with a high or low teen birth rate, respectively.[87]

Khan and colleagues (2017) identified a total of 44 outliers in 2003: 30 counties had a high teen birth rate surrounded by counties with a low teen birth rate, and 14 counties had a low teen birth rate surrounded by counties with a high teen birth rate. In 2012, Khan and colleagues identified 40 outliers: 24 counties had a high teen birth rate surrounded by a low teen birth rate and 16 counties had a low teen birth rate surrounded by a high birth rate.[87]

A summary of the findings from both studies is presented in Table 7.

Table 7: Summary of findings

Study Details	Antonelli et al. (2013)	Khan et al. (2017)
Objective	Detect clinical practice anomalies in health-related databases	Identify spatial outliers of teenage birth rate in US counties
Framework/Methodology	Patterns in medical records compared to published medical guidelines. Anomalies were	Anselin Local Moran's I cluster and outlier analysis method. Spatial outliers were identified based on high or

	identified when patterns did not adhere to guidelines.	low teen birth rates contrasted with surrounding counties' rates.
Data Source	Patient data from 905 pregnant persons	National Vital Statistics System Birth Data files between 2003-2012
Primary Guidelines/Data Reference	Italian Ministry of Health (Ministerial Decree, 1998) for antenatal visits	Teen births at a county level
Main Findings	Two main anomaly patterns: 1) Underutilization of free examinations. 2) Higher frequency of examinations in the 2nd and 3rd trimesters than recommended.	44 outliers in 2003: 30 counties with high birth rates contrasted by surrounding low rates, 14 with low rates contrasted by surrounding high rates. In 2012, 24 counties with high birth rates contrasted by surrounding low rates, 16 the other way around.
Method of Identifying Anomalies/Outliers	Any antenatal visit pattern differing from the medical guidelines	Spatial outliers using positive non-zero weights assigned to the eight closest neighbours to the target county.
Total Anomalies/Outliers Reported	Not Quantitatively Described	44 outliers in 2003 and 40 outliers in 2012
Outliers type	Point outliers	Point outliers

Outliers measure	Information	Distance
Outliers root cause	Unclear	Unclear

3.11 Discussion

The philosophy of science has long grappled with the concept of scientific discovery and the methodologies leading to such insights. Prominent 17th-century thinkers, including Bacon, Descartes, and Newton, posited that specific methods of inquiry would lead not just to discoveries but also to unearthing definitive intellectual truths.[88] However, the 19th century witnessed a wane in these conventional inquiry methods, attributed to influences like Romanticism and the inadequacy of prior models to propel scientific progress. This evolution, coupled with advancements in mathematical and statistical techniques, birthed the now-prevailing hypothetico-deductive model, which prioritizes the testing of falsifiable hypotheses over their genesis.[88]

Clinical research predominantly adheres to the hypothetico-deductive model, as evidenced by the widespread adoption of the null and alternative hypothesis in comparative clinical research and the elevated status of randomized controlled trials as the gold standard.[89] Yet, clinical research distinguishes itself with the tenet of clinical equipoise, which mandates the justification of the rationale and beliefs underpinning a hypothesis.[90]

Notably, clinical research isn't the sole field that underscores the genesis of a hypothesis. Data-driven discovery, a method frequently employed in domains like genomics and astronomy, emphasizes gleaning insights straight from vast datasets. Standing in contrast to traditional hypothesis-driven methods, this approach gives precedence to the data itself as the foundational basis.[91-94]

Increasing the rate of clinical discoveries will inevitably lead to better therapeutics, diagnostics, and patient care. The existing practices in identifying, investigating, and communicating unusual clinical observations through case reports and case studies are inefficient, resource-intensive, and do not utilize existing technologies. In this article, we proposed a framework for using patient data, applying outlier analysis, and investigating outliers to accelerate the rate of clinical discoveries. We have presented a non-technical introduction to outlier analysis, with applicable

clinical examples, to allow for an intuitive understanding of the process by healthcare professionals.

The use of outlier analysis methods to detect suspicious data and abnormal cases for further clinical investigation may have been first suggested in a publication in the year 2000 by Laurikkala and colleagues.[83] We were unable to find further published literature that suggests using outlier analysis with the input of content-matter experts to uncover novel clinical observations.

The use of various data analytics approaches to support or augment a traditional human process is a cornerstone of augmented intelligence and symbiotic autonomous systems.[95] As stated by Broschert and colleagues (2019), part of the promised applications of augmented intelligence is the "medical analysis of case files to identify efficient treatment options."[95] We provided here a detailed, step-by-step process on how to utilize generic statistical and machine-learning approaches in augmenting all aspects of clinical discovery. We built our framework explicitly to simulate the classic clinical and bedside process of discovery that has already contributed immeasurably to medicine. This framework has the potential to rapidly accelerate the classic clinical discovery process. We envision that this framework could be used with both existing data from clinical studies, as well as live data from patient records or ongoing clinical trials. A research unit could be designated to build and maintain the model and the outlier analysis measure, while a committee of domain experts could continuously investigate identified outliers. This process could run perpetually and generate continuous insights for both quality assurance and control of the data, as well as for identifying promising areas of study to be investigated. In addition, such a framework would reduce human bias toward pursuing certain unusual clinical observations over others. Furthermore, the structured approach of this framework opens the opportunity for collaboration and synthesis of clinical discovery across various groups, as each of the steps outlined can be replicated and measured.

Recognizing the potential of accelerating clinical discoveries in obstetrics — a field that has been traditionally neglected by the pharmaceutical industry — we conducted a systematic review to explore the existing use of outlier analysis in obstetric research. Our systematic review identified two obstetrics-related studies that utilized outlier analysis for the purposes of outlier detection. Both studies assessed outliers at an aggregate level rather than at an individual patient level.

Neither study utilized a predictive model to represent a normal behaviour for which an observation is contrasted to determine its outlier status. Instead, one study used clinical guidelines as the expected normal behaviour, while the other study used the k-nearest neighbours algorithm approach — a particular outlier analysis approach that is best suited for graphical data as opposed to multidimensional data (e.g., patient data).

To our knowledge, this is the first systematic review of outlier detection studies in obstetric research. In 2011, Gaspar and colleagues performed a systematic review of outlier detection techniques in medical administrative data. Gaspar and colleagues identified 177 papers for inclusion but reported on 80 randomly selected papers. The authors' findings suggest that the majority of the reported papers were in the fields of oncology (32%), quality indicators (24%), genetics (15%), and neurology (12%).[39] The primary papers in Gaspar et al. indicate that outlier analysis has been successfully used to identify gene targets in prostate cancer,[96] drive insights as to the reasons behind long hospital admissions in patients with heart failure,[97] and improve data quality in medical registries.[98] Outlier analysis is sometimes discussed under the topic of data mining, whereby the aim of the discipline is to uncover useful information and knowledge that is hidden in large amounts of data.[99] Data mining has been widely used as an exploratory analysis tool to uncover hidden associations in clinical databases.[100-108]

Limitations to our systematic review include the restriction of the search strategy to the English language, which may have missed publications in other languages. Another limitation is the lack of standardized definitions and the interdisciplinary nature of outlier analysis methods. This lack of standard terminology and the large number of disciplines utilizing outlier analysis with potentially different terminology may have hindered our search strategy and screening efforts, whereby terminology that did not conform to the reviewers' expectations may have been missed. Finally, there is no standard method to assess the quality of outlier studies. This limited our ability to conduct an assessment of the quality of the included studies.

In a paper published after the systematic review's search date, we applied the Augmented Intelligence framework to data on hypertensive disorders of pregnancy from the FACT randomized controlled trial (N = 2,301) and the OaK prospective cohort study (N = 8,085). Using a random forest predictive model, we predicted preeclampsia and other hypertensive disorders, marking those misclassified with over 90% confidence as outliers. This method,

termed extreme misclassification contextual outlier (EMCO) analysis, was compared to the traditional isolation forest outlier method. Out of the 302 outliers, clinical experts identified 49 as representing potential novelties. The EMCO method pinpointed 111 (1.1%) outliers, in contrast to the 191 (1.8%) from the isolation forest. Notably, EMCO identified a higher proportion of potential novelties (37.8%) than the isolation forest (3.7%). Within the EMCO method, the FACT study model outperformed the OaK model. While OaK had more outliers at 98 (1.2%) compared to FACT's 13 (0.6%), FACT had a higher rate of potential novelties (76.9%) than OaK (32.7%).[109]

3.12 Conclusion

Outlier analysis can be utilized to fuel the classic process of clinical discovery in an augmented intelligence framework. The classic approach to clinical discovery has been largely human-based. Our augmented intelligence framework provides a structured and multidisciplinary approach that can be implemented with any patient data. The aim of our framework is to accelerate the rate of clinical discovery through the use of outlier analysis. The increased efficiency will likely provide a greater rate of novel and promising insights. The field of obstetrics can particularly benefit from implementing this framework, given the chronic exclusion of pregnant individuals from biopharmaceutical studies, but methods for application in obstetrics research currently require ongoing development.

3.13 Disclosure of Interests

Authors disclose no competing interests.

3.14 Appendix A – Search Strategy

Ovid Embase Classic+Embase AND Ovid MEDLINE(R) ALL

1 obstetric*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, say]

2 Pregnan*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

3 maternal.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

4 materno$fetal.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

5 neonatal.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

6 1 or 2 or 3 or 4 or 5

7 outlier*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

8 anomal*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

9 novelty.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

10 signal*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, Sy]

11 clinical.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

12 case.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

13 fraud*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

14 (machine adj learning).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]

15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16 analysis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

17 detection.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

18 discovery.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]

19 Algorithm.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]

20 16 or 17 or 18 or 19

21 ((outlier* or anormal* or novelty or signal* or clinical or case or fraud* or (machine adj learning)) adj (analysis or detection or discovery or Algorithm)).mp.

22 6 and 21

23 limit 22 to humans

24 limit 23 to english language

Web of Science (Classic)

1 ALL=(obstetric*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

2 ALL=(Pregnan*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

3 ALL=(maternal)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

4 ALL=(materno$fetal)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

5 ALL=(neonatal)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

6 #5 OR #4 OR #3 OR #2 OR #1

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

7 TI=(outlier*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

8 TI=(anomal*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

9 TI=(novelty)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

10 TI=(signal*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

11 TI=(clinical)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

12 TI=(case)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

13 TI=(fraud*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

14 TI=(machine NEAR learning)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

15 #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

16 TI=(analysis)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

17 TI=(detection)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

18 TI=(discovery)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

19 TI=(Algorithm)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

20 #19 OR #18 OR #17 OR #16

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

21 #20 AND #15 AND #6

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

22 (#21) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

3.15 Appendix B – List of Excluded Studies With Reason — Post–Full-Text Screening

Study Reason for Exclusion

Allotey PA and Harel O (2019). "Multiple Imputation for Incomplete Data in Environmental Epidemiology Research."[110] Methods do not match the required eligibility criteria.

Bate A (2007). "Bayesian Confidence Propagation Neural Network."[111] Methods do not match the required eligibility criteria.

Bengtson AM et al. (2016). "Multiple Overimputation to Address Missing Data and Measurement Error: Application to HIV Treatment During Pregnancy and Pregnancy Outcomes."[112] Methods do not match the required eligibility criteria.

Boland MR et al. (2017). "Development of A Machine Learning Algorithm to Classify Drugs of Unknown Fetal Effect."[113] Methods do not match the required eligibility criteria.

Cardoso-dos-Santos AC et al. (2018). "Twin Peaks: A Spatial and Temporal Study of Twinning Rates in Brazil."[114] Methods do not match the required eligibility criteria.

Chauvet PE et al. (2014). "Evaluation of Automatic Feature Detection Algorithms in EEG: Application to Interburst Intervals."[115] Methods do not match the required eligibility criteria.

Chen HC et al. (2013). "Data Mining for Signal Detection of Adverse Event Safety Data."[116] Population does not match the required eligibility criteria.

Ferguson KK et al. (2018). "Foetal Ultrasound Measurement Imputations Based on Growth Curves Versus Multiple Imputation Chained Equation (MICE)."[117] Methods do not match the required eligibility criteria.

Feyaerts D et al. (2018). "Endometrial Natural Killer (NK) Cells Reveal a Tissue-Specific Receptor Repertoire."[118] Methods do not match the required eligibility criteria.

Giezen TJ et al. (2010). "Mapping the Safety Profile of Biologicals: A Disproportionality Analysis Using the Who Adverse Drug Reaction Database, Vigibase."[119] Methods do not match the required eligibility criteria.

Harel O et al. (2018). "Multiple Imputation for Incomplete Data in Epidemiologic Studies."[120] Methods do not match the required eligibility criteria.

Karayiannis NB et al. (2006). "Automated Detection of Videotaped Neonatal Seizures Based on Motion Tracking Methods."[121] Population does not match the required eligibility criteria.

Lyles RH and Allen AS (2002). "Estimating Crude or Common Odds Ratios in Case-Control Studies with Informatively Missing Exposure Data."[122] Methods do not match the required eligibility criteria.

Menon R et al. (2014). "Multivariate Adaptive Regression Splines Analysis to Predict Biomarkers of Spontaneous Preterm Birth."[123] Methods do not match the required eligibility criteria.

Noto K et al. (2015). "CSAX: Characterizing Systematic Anomalies in eXpression Data."[124] Population does not match the required eligibility criteria.

Padmavathy S and Suresh P (2019). "Fetal Ultrasound Image Evaluation of Chromosomal Anomaly Detection and Classification Using Conditional Rooted Neural Network (CRNN)."[125] No full text was obtainable.

Perkins NJ et al. (2018). "Principled Approaches to Missing Data in Epidemiologic Studies."[126] Methods do not match the required eligibility criteria.

Sairanen V et al. (2018). "Fast and Accurate Slicewise OutLIer Detection (SOLID) With Informed Model Estimation for Diffusion MRI Data."[127] Population does not match the required eligibility criteria.

Sbrollini A et al. (2018). "eCTG: An Automatic Procedure to Extract Digital Cardiotocographic Signals from Digital Images."[128] Methods do not match the required eligibility criteria.

Stevens J et al. (2014). "Effects of Changes in Click-Evoked Otoacoustic Emission (CEOAE) Pass Criteria, As Used in the English Newborn Hearing Screening Program, on Screening Outcome."[129] Methods do not match the required eligibility criteria.

Sun H et al. (2019). "Identification of Suspicious Invasive Placentation Based on Clinical MRI Data Using Textural Features and Automated Machine Learning."[130] Methods do not match the required eligibility criteria.

Temko A and Lightbody G (2016). "Detecting Neonatal Seizures with Computer Algorithms."[131] Population does not match the required eligibility criteria.

Temko A et al. (2011). "EEG-Based Neonatal Seizure Detection with Support Vector Machines."[132] Population does not match the required eligibility criteria.

Temko A et al. (2011). "Performance Assessment For EEG-Based Neonatal Seizure Detectors."[133] Population does not match the required eligibility criteria.

Tilling K et al. (2016). "Appropriate Inclusion of Interactions Was Needed to Avoid Bias in Multiple Imputation."[134] Methods do not match the required eligibility criteria.

Turnbull JP et al. (2001). "Automated Detection of Trace Alternant During Sleep in Healthy Full-Term Neonates Using Discrete Wavelet Transform."[135] Population does not match the required eligibility criteria.

Varanini M et al. (2017). "A New Method for QRS Complex Detection in Multichannel ECG: Application to Self-Monitoring of Fetal Health."[136] Methods do not match the required eligibility criteria.

Wang WL and Lin TI (2014). "Multivariate T Nonlinear Mixed-Effects Models for Multi-Outcome Longitudinal Data With Missing Values."[137] Methods do not match the required eligibility criteria.

Wright DB and London K (2009). "Multilevel Modelling: Beyond the Basic Applications."[138] Methods do not match the required eligibility criteria.

Yu Q et al. (2018). "Automatic Identifying of Maternal ECG Source When Applying ICA in Fetal ECG Extraction."[139] Methods do not match the required eligibility criteria.

Zhao LP et al. (1996). "Regression Analysis with Missing Covariate Data Using Estimating Equations."[140] Methods do not match the required eligibility criteria.

Ziegler A et al. (2003). "Analysis of Pregnancy and Other Factors on Detection of Human Papilloma Virus (HPV) Infection Using Weighted Estimating Equations for Follow-Up Data."[141] Methods do not match the required eligibility criteria.

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1.

4 CHAPTER 4: THIRD COMPONENT ARTICLE (PUBLISHED)

Augmented Intelligence for Clinical Discovery in Hypertensive Disorders of Pregnancy Using Outlier Analysis

4.1 Article Preface

Chapter 2 emphasized the need for a more efficient approach to clinical discovery. We proposed such an approach in Chapter 3 with a review of the methods associated with the approach and how such methods have been used in obstetrics. In this chapter, we present a published article in which we implemented the framework discussed in Chapter 3 onto two separate datasets and compare our proposed outlier analysis methods to the results of a more traditional approach in outlier analysis. The published article in this chapter aims to address this thesis's fourth objective: 4. To apply the framework on data from the Folic Acid Clinical Trial (FACT) and the Ottawa and Kingston (OaK) Birth Cohort — two datasets that assessed preeclampsia and hypertensive disorders of pregnancy.

GJ contributed to the conception, design, analysis, interpretation, drafting, and revision of the work. DF contributed to the conception, design, interpretation, and revision of the work. JR contributed to the conception, design, interpretation, and revision of the work. AF contributed to the conception, design, interpretation, and revision of the work. RG contributed to the conception, design, interpretation, and revision of the work. MR contributed to the acquisition of the data and revision of the work. GS contributed to the acquisition of the data and revision of the work. TC contributed to the conception, design, interpretation, and revision of the work. MW contributed to the conception, design, analysis, interpretation, and revision of the work.

The article has been published in the *Cureus Journal of Medical Science* and can be found here: Cureus | Augmented Intelligence for Clinical Discovery in Hypertensive Disorders of Pregnancy Using Outlier Analysis | Article. The article can be cited as: Janoudi G, Fell D B, Ray J G, et al. (March 30, 2023) Augmented Intelligence for Clinical Discovery in Hypertensive Disorders of Pregnancy Using Outlier Analysis. Cureus 15(3): e36909. doi:10.7759/cureus.36909.

4.2 Title

Augmented Intelligence for Clinical Discovery in Hypertensive Disorders of Pregnancy Using Outlier Analysis

4.3 Authorship

Ghayath Janoudi,[1,2] Deshayne B. Fell,[1,3] Joel G. Ray,[4] Angel M. Foster,[5] Randy Giffen,[6] Tammy J. Clifford,[7,1] Marc A. Rodger,[8,2] Graeme N. Smith,[9,10] Mark C. Walker[2,1,11,12,13,14]

4.4 Author Affiliations

1 Epidemiology and Public Health, University of Ottawa, Ottawa, CAN
2 Clinical Epidemiology, Ottawa Hospital Research Institute, Ottawa, CAN
3 Maternal and Neonatal Research, Children's Hospital of Eastern Ontario, Ottawa, CAN
4 Medicine, Health Policy Management and Evaluation, and Obstetrics and Gynecology, Saint Michael's Hospital, Toronto, CAN
5 Health Sciences, University of Ottawa, Ottawa, CAN
6 Medical Research, International Business Machines (IBM) Corporation, Ottawa, CAN
7 Research, Canadian Institute of Health Research, Ottawa, CAN
8 Medicine, McGill University, Montreal, CAN
9 Obstetrics and Gynecology, Kingston General Hospital, Kingston, CAN
10 Biomedical and Molecular Sciences, Queen’s University, Kingston, CAN
11 Maternal and Neonatal Research, University of Ottawa, Ottawa, CAN
12 Obstetrics and Gynecology, University of Ottawa, Ottawa, CAN
13 Obstetrics, Gynecology, and Newborn Care, The Ottawa Hospital, Ottawa, CAN
14 Maternal and Neonatal Research, Children’s Hospital of Eastern Ontario, Ottawa, CAN

4.5 Correspondence

Ghayath Janoudi

4.6 Abstract

4.6.1 Objectives

Clinical discoveries are heralded by observing unique and unusual clinical cases. The effort of identifying such cases rests on the shoulders of busy clinicians. We assess the feasibility and applicability of an augmented intelligence framework to accelerate the rate of clinical discovery

in preeclampsia and hypertensive disorders of pregnancy ― an area that has seen little change in its clinical management.

4.6.2 Methods

We conducted a retrospective exploratory outlier analysis of participants enrolled in the Folic Acid Clinical Trial (FACT; N = 2,301) and the Ottawa and Kingston (OaK) Birth Cohort (N = 8,085). We applied two outlier analysis methods: extreme misclassification contextual outlier and isolation forest point outlier. The extreme misclassification contextual outlier is based on a random forest predictive model for the outcome of preeclampsia in FACT and hypertensive disorder of pregnancy in OaK. We defined outliers in the extreme misclassification approach as mislabelled observations with a confidence level of more than 90%. Within the isolation forest approach, we defined outliers as observations with an average path length z score less or equal to -3, or more or equal to 3. Content experts reviewed the identified outliers and determined if they represented a potential novelty that could conceivably lead to a clinical discovery.

4.6.3 Results

In the FACT study, we identified 19 outliers using the isolation forest algorithm and 13 outliers using the random forest extreme misclassification approach. We determined that three (15.8%) and 10 (76.9%) were potential novelties, respectively. Out of 8,085 participants in the OaK study, we identified 172 outliers using the isolation forest algorithm and 98 outliers using the random forest extreme misclassification approach; four (2.3%) and 32 (32.7%), respectively, were potential novelties. Overall, the outlier analysis part of the augmented intelligence framework identified a total of 302 outliers. These were subsequently reviewed by content experts, representing the human part of the augmented intelligence framework. The clinical review determined that 49 of the 302 outliers represented potential novelties.

4.6.4 Conclusions

Augmented intelligence using extreme misclassification outlier analysis is a feasible and applicable approach for accelerating the rate of clinical discoveries. The use of an extreme misclassification contextual outlier analysis approach has resulted in a higher proportion of potential novelties than using the more traditional point outlier isolation forest approach. This finding was consistent in both the clinical trial and real-world cohort study data. Using

augmented intelligence through outlier analysis has the potential to speed up the process of identifying potential clinical discoveries. This approach can be replicated across clinical disciplines and could exist within electronic medical records systems to automatically identify outliers within clinical notes to clinical experts.

4.6.5 Categories

Obstetrics/Gynecology, Health Care Technology, Epidemiology/Public Health

4.6.6 Keywords

Real-world data, clinical trials, research methods and design, augmented intelligence, HDP, preeclampsia treatment, clinical discovery, hypertensive disorders of pregnancy, preeclampsia-eclampsia

4.7 Introduction

Hypertensive disorders of pregnancy, including preeclampsia, are a leading cause of maternal and perinatal morbidity and mortality globally.[1] Despite considerable advancements in elucidating its pathophysiology, the management of preeclampsia has changed minimally over the past two decades.[2-7] Clinical trials of preeclampsia prevention have largely not shown positive results, except for Aspirin in the prevention of early-onset preeclampsia.[8-10]

Yet clinical observations play a pivotal role in the advancement of medical knowledge.[11-13] The description of an individual clinical case is sometimes the catalyzing step in generating new clinical research by describing its aberrant or peculiar nature, and the formulation of a hypothesis of why this is so.[12-18] The latter was evident during the COVID-19 pandemic, i.e., in understanding the natural history of COVID-19, its detection, and its clinical management.[19-23]

Case reports and case series are the conventional study design used by clinicians and researchers to communicate a novel clinical discovery.[16-18] However, their recording and documentation depend on the busy clinician's power of observation,[24,25] and the prioritization by the journal editors who tend to offer case reports and case series low priority on the evidence-based medicine hierarchy of publication. Hence, case reports are now mostly used as educational tools.[26-28]

Instead of relying on conventional and anecdotal case reports or case series, augmented intelligence uses a machine-based analytic approach to identify potentially new clinical discoveries and flag these to a human content-matter expert. The analytical part of augmented intelligence comprises any statistical or machine-learning method, including outlier analysis. Outlier analysis is currently used for financial fraud detection, network connection anomalies, malware detection, and manufacturing quality control.[29,30] It encompasses various statistical and machine-learning approaches that aim to identify observations that deviate significantly from the majority of other observations.[29,30] In health sciences research, outliers were conventionally handled as statistical noise and were excluded from analyses.[31] However, some outliers may arise from an unrealized and important mechanism or "signal" that holds valuable information and is, thus, worthy of further exploration.[29,32]

Our study evaluated contextual outlier analysis using extreme misclassification to discover potentially new phenomena about preeclampsia and hypertensive disorders of pregnancy, using data from a completed randomized clinical trial and a separate cohort study. Extreme misclassification identifies observations that a predictive model mislabels with high confidence as outliers. In addition, the performance of the extreme misclassification contextual outlier analysis was contrasted with a more traditional point outliers detection algorithm to assess which can more aptly identify an outlier potentially useful for clinical discovery.

4.8 Materials and Methods

We conducted a retrospective exploratory outlier analysis of patients enrolled in the Folic Acid Clinical Trial (FACT) and the Ottawa and Kingston (OaK) Birth Cohort studies. FACT was designed to capture preeclampsia diagnosis and progression and thus had a well-structured and focused dataset specific to preeclampsia. The OaK, as a prospective cohort study, represented the real world that aimed to capture myriad pregnancy complications, which may more accurately represent data gathered in usual clinical settings.[8,33]

We used two methods within each dataset to identify outliers: isolation forest (a traditional point outliers approach) and extreme misclassification through a random forest predictive model (a contextual outlier approach).

As we are utilizing a predictive model development approach in our contextual outliers method (using the random forest outlier analysis approach), we followed the transparent reporting of a

multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement for reporting (i.e., transparent reporting of a multivariable prediction model for individual prognosis or diagnosis).[34]

4.8.1 Data Sources and Description of Participants

The FACT was a multi-national, double-blind, randomized, placebo-controlled trial completed in Argentina, Australia, Canada, Jamaica, and the UK. It aimed to assess the effects of a 4 mg daily folic acid supplementation on the development of preeclampsia in a high-risk obstetrics population. Between April 2011 and November 2015, a total of 2,464 participants were randomized in a 1:1 ratio to either folic acid or placebo. A total of 2,301 participants were included in the intent-to-treat analysis, with 14.1% of all participants developing new-onset preeclampsia.[8]

The OaK was a prospective cohort study conducted from October 2002 to April 2009 that enrolled Canadian pregnant individuals at 12 to 20 weeks gestation who had a viable singleton or twin pregnancy. Data were systematically captured about maternal and infant demographics, maternal health, obstetrical history, and major pregnancy outcomes. One of these outcomes was an adjudicated outcome of hypertensive disorders of pregnancy. A total of 598 participants (7.4%) experienced a hypertensive disorder during pregnancy.[33]

4.8.2 Study Outcomes in FACT and OaK

The primary outcome of FACT, and that we used herein for the development of a predictive model, was the presence or absence of preeclampsia. Preeclampsia was defined as one of the following: 1) a diastolic blood pressure of ≥ 90 mm Hg on two occasions, four hours or more apart, and proteinuria (more than ++ on dipstick, 24-hour urinary protein ≥ 300 mg, or random protein creatinine ratio ≥ 30 mg protein/mmol), each arising at 20+ weeks' gestation; 2) development of the HELLP syndrome; or 3) superimposed preeclampsia namely, a history of pre-existing hypertension before 20 weeks gestation, with new-onset proteinuria at 20+ weeks.[8,35]

The OaK cohort evaluated the adjudicated outcome of hypertensive disorders of pregnancy, which included chronic hypertension during pregnancy, pregnancy-induced hypertension, preeclampsia, and HELLP syndrome. The outcome was also used herein.[33]

4.8.3 Features Engineering

All FACT and OaK variables were used in our study with the exception of those meeting any of the following criteria: 1) a variation or a sub-categorization of the outcome; 2) a variable with over 50% missing data; 3) a variable used to re-categorize an existing continuous variable (e.g., age group when age was present); 4) a variable with only one unique value to all participants (e.g., death when no deaths occurred); 5) a variable whereby one unique value is present for 99% or more of all observations.

Considering our aim of identifying potential clinical discoveries through outlier analysis, we did not perform further data cleaning.

4.8.4 Sample Size

As the sample sizes for FACT and OaK were fixed, no formal sample size calculation was completed for the current analyses. All 2,301 intent-to-treat participants in the FACT trial were included in our analyses, as well as all 8,085 participants from the OaK cohort.[8,33]

4.8.5 Missing Data

The overarching imputation strategy for missing data was that they were missing at random. We utilized an iterative imputation approach whereby missing data were imputed via a regression model by treating variables with missing data as a function of other variables. Iterative imputation performs this function in an iterated round-robin fashion in which a variable is designated as the dependent variable and the rest of the variables are designated as independent variables. This is done for every variable with missing data and repeated for a total of 10 iterations. The final imputation is the result of the tenth round.[36-38]

We applied an exception to the previous imputation approach when it was clear that the missing data were due to a non-random mechanism. This includes missing data due to non-applicable questions i.e., those questions not posed to certain participants following a previous exclusionary question. This group of missing data cannot be assumed to be missing at random. In these cases, we introduced a numeric value to represent the lack of applicability for a continuous variable (for example, a zero in the case of a number of cigarettes), or a new category in the case of a categorical variable.

4.8.6 Outlier Analysis Methods

We analyzed each dataset for outliers using two approaches: the isolation forest, and extreme misclassification based on a random forest predictive model.

4.8.6.1 Isolation Forest

Isolation forest is an ensemble outlier detection recursive algorithm that works by assuming that the number of outliers is small and that they are easily isolated from the rest of the sample. This is conducted through a recursive process, whereby a variable is picked and portioned at random until all observations have been isolated individually. This process produces a decision tree structure in which the path length from the first split until the isolation of the observation can be measured. This process takes place across all variables until all observations have been isolated in all variables, at which point an average path across all variables is calculated for each observation.[39] We determined extreme outliers as observations with an average path length (also known as anomaly score) z score ≤ -3, or ≥ 3, using the programming language Python 3.9 (Python Software Foundation, Wilmington, DE, USA), together with NumPy, Pandas, and the Scikit-Learn software packages.[40-43] We tuned the isolation forest n_estimators and max_samples parameters by choosing the first value at which the mean and SD of the anomaly score showed the least variations beyond that value, starting from a value of 100 n_estimator and 256 max_samples. For the contamination parameter, which provides the model with an assumption of the extent of outliers to be expected in the sample, it was assumed that no more than 5% of the sample could potentially be an outlier, i.e., the contamination value was set at 0.05. Finally, we chose a random state value of 2022, namely, the year in which this analysis was conducted.[40,43-45]

4.8.6.2 Random Forest

This second outlier approach required the development of a predictive model using the random forest algorithm and then leveraging the misclassified observations that the model wrongly predicted with a high level of confidence as an indicator of an outlier status (denoting extreme misclassification). The random forest algorithm is a widely used ensemble learning model in which several base estimators develop decision trees based on a random set of observations and a random set of variables, classifying the observation to the outcome of interest. The collective classification of all the base estimators forms the observation's final prediction.[46] To train, test, and validate the random forest model, the FACT dataset was split into a training set (with 1,200

observations), a testing set (with 800 observations), and a validation set (with 301 observations). Similarly, we split the OaK data into training, testing, and validation sets with 3,600, 2,400, and 2085 observations, respectively. We chose the parameters of the model through a random grid search approach, followed by a targeted grid approach that was informed by the results of the random grid search.

We considered those observations that the random forest model misclassified with a confidence level over 0.90 (90%) as outliers. The random forest confidence level represents the proportion of the base learners (or individual trees) that voted for the class. A threshold of 0.90 is an appropriately high threshold to allow for the capture of potentially novel observations whereby the possibility of an unmeasured but influential underlying mechanism could have been the cause of such misclassification.

We then constructed case narrative reports for the identified outliers by returning to the original datasets. Two content-expert researchers (GJ and MW) examined these case narratives and determined if an outlier had the potential of being a novel observation. We assessed each case narrative through several clinical considerations, as well as the clinical likelihood of experiencing the outcome, given the available information. Specifically, the two reviewers asked three basic questions when reviewing each observation: 1) Is the presentation of the pregnant individual and the pregnancy journey likely to have led to the observed outcome?; 2) Are there any recorded potential effect modifiers that may have influenced the likely course of pregnancy and the resulting pregnancy outcome?; and 3) Is there any indication of potentially strong effect modifiers that are not recorded, such as an unrecorded medication or an undocumented chronic disease?

For a better understanding of the assessment process, see Table 8, where we present fictitious examples of case narrative assessments (actual case narratives are not publicly available to safeguard participants' privacy and data).

Table 8: Fictitious Example of Clinical Assessment of Outliers

ID	Assessment	Reasoning	Risk Factors	Interesting Variables
123-456	Potential novelty	The participant had PE, BP measured at 187/103 mm HG, elevated LFT, and required delivery at 34 weeks gestation. The number and type of risk factors do not necessarily justify this presentation. Also, the participant suffers from depression and indicated concomitant medication. Could the concomitant medication predispose the participant to the observed outcome? This would be worth further examination.	Overweight (BMI 29), new partner	SSRIs in concomitant medication, no perinatal vitamins
123-678	Natural deviation	The participant exhibited PE with BP at 140/90 mm HG and 3+ urine dipstick. The participant delivered at 39 weeks gestation with no complications. Considering existing risk factors and positive overall maternal and fetal outcomes, this clinical scenario is not unexpected.	Previous history of PE, obesity (BMI 33), advanced maternal age	Aspirin, folic acid, calcium supplements

BP = blood pressure; LFT = liver function test; PE = pulmonary embolism; SSRIs = selective serotonin reuptake inhibitors.

Based on the clinical review (completed by GJ and MW), we classified each observation as either a "potential novelty" or a "natural deviation." We also attempted to explain why either type of observation was captured as an outlier in its given model. Based on this assessment, we reported the proportion of potential novelties detected by each algorithm within each dataset.

4.9 Results

4.9.1 Characteristics of Participants in FACT and OaK

Participants in both studies were of similar age and shared similar prior pregnancy characteristics such as gravidity and multiple pregnancies. Participants in the FACT study had more risk factors for preeclampsia than those enrolled in OaK, including a higher mean weight (91.6 versus 70.4 kg), a higher proportion of multiple pregnancies (18.6% versus 1.4%), past hypertension (18.4% versus. 1.3%), and a history of preeclampsia (25.3 versus 2.9%), respectively (Table 9).

Table 9: Maternal and Medical Characteristics of the FACT and OaK Participants

Variable	FACT (N = 2,301)	OaK (N = 8,085)
Age in years, mean (SD)	31.4 (5.3)	30.3 (5.3)
Weight in kg, mean (SD)	91.6 (24.8)	68.7 (19.9)
Height in cm, mean (SD)	NA	163.7 (14.4)
Body mass index in kg/m^2, mean (SD)	34.0 (11.2)	NA
G (gravidity), median (interquartile range)	2 (2 to 4)	2 (1 to 3)
T (number of term births), median (interquartile range)	1 (0 to 1)	1 (0 to 1)
P (number of preterm births), median (interquartile range)	0 (0 to 0)	0 (0 to 0)
A (number of abortions/miscarriage), median (interquartile range)	0 (0 to 1)	0 (0 to 2)
L (number of living children), median (interquartile range)	1 (0 to 1)	1 (0 to 1)
M (number of multiple pregnancies), median (interquartile range)	0 (0 to 0)	0 (0 to 0)
Current multiple pregnancy, n (%)	428 (18.6)	361 (4.5)
Assisted reproductive technology pregnancy, n (%)	213 (9.3)	359 (4.4)
History of chronic hypertension, n (%)	428 (18.6)	101 (1.3)
History of gestational diabetes, n (%)	NA	141 (1.7)
History of diabetes mellitus, n(%)	311 (13.5)	NA
History of preeclampsia, n (%)	581 (25.3)	237 (2.9)
History of smoking, n (%)	919 (39.9)	766 (9.5)
Smoking during pregnancy, n (%)	173 (7.5)	NA
Alcohol use during pregnancy, n (%)	48 (2.1)	NA
Folic acid supplementation (not intervention related), n (%)	1,882 (81.8)	1,786 (22.1)
Aspirin, n (%)	665 (28.9)	NA
Calcium supplementation, n (%)	196 (8.5)	NA
Other medications, n (%)	1,620 (70.4)	2,740 (33.9)

FACT = Folic Acid Clinical Trial; NA = not applicable; OaK = Ottawa and Kingston Birth Cohort; SD = standard deviation.

There were no missing data for the outcomes assessed in the random forest model in either dataset. The FACT study contributed a total of 84 variables in both the random forest and isolation forest models; of these, 34 variables had missing values. The OaK cohort contributed a total of 72 variables to the random forest and isolation forest models; of these, 48 variables had missing values. Missing data were handled according to the missing data imputation plan described previously.

4.9.2 Model Development, Specification, and Performance

4.9.2.1 Isolation Forest

Tuning the isolation forest model produced the following parameters for FACT (N=2,301) data: n_estimator = 300, max_samples = 700. And it produced the following parameters for OaK (N=8,085) data: n_estimator = 900 and max_samples = 256. As per our methods, we used the value of 2,022 as our random_state and 0.05 for contamination. The remaining tuning parameters were left at default values (bootstrap = False, max_features = 1.0, n_jobs = None, warm_start = False). The model generated an anomaly score for each observation, which we used as the basis to determine outliers.

As the isolation forest is an unsupervised model, outcome-based model performance measures could not be calculated.

4.9.2.2 Random Forest

The FACT dataset included 2,301 participants, 325 (14.1%) of who experienced the outcome of preeclampsia. The OaK dataset included 8,085 participants; 597 (7.4%) experienced the outcome of hypertensive disorders during pregnancy. Tuning the FACT model resulted in the following parameters: bootstrap = False, max_depth = 10, max_features = 40, min_samples_leaf = 2, min_samples_split = 2, and n_estimators = 600. Tuning the model for OaK resulted in the following parameters: n_estimators = 100, min_samples_split = 6, min_samples_leaf = 1, max_features = 10, max_depth = 90, and bootstrap = False.

Using the validation dataset, the FACT random forest model showed a precision of 0.97 and a recall of 0.83 for the outcome of preeclampsia. The OaK random forest model showed a precision of 0.75 and a recall of 0.08 for the outcome of hypertensive disorders of pregnancy. The performance of the models over the entirety of the FACT and OaK datasets is displayed in Table 10

Table 10: Classification Report Metrics for Random Forest Model Applied on the Full Dataset (Training, Test, and Validation Sets)

Class	FACT Precision	FACT Recall	OaK Precision	OaK Recall
No outcome* present	0.99	0.99	0.96	1.00
Outcome* present	0.95	0.93	0.97	0.50

FACT = Folic Acid Clinical Trial; OaK = Ottawa and Kingston Birth Cohort.
* The FACT outcome was preeclampsia or hemolysis, elevated liver enzymes, low platelets (i.e., HELLP) syndrome. The OaK outcome was a hypertensive disorder of pregnancy.

4.9.3 Description of Outliers

4.9.3.1 Isolation Forest

Based on setting outliers at a z score of ≤ -3 or ≥ 3, 19 outliers (0.8%) were identified in the FACT dataset and 172 outliers (2. 1%) were identified in the OaK dataset.

Outliers in each of the datasets display different sets of participants' baseline and demographic characteristics that set them apart from their original datasets. These characteristics are outlined in Table 11.

Table 11: Characteristics of Isolation Forest and Random Forest Outliers and Their Original Datasets

Variable	FACT Isolation Forest Outliers (N = 19)	FACT Random Forest Outliers (N = 13)	Original FACT Dataset (N = 2,301)	OaK Isolation Forest Outliers (N = 172)	OaK Random Forest Outliers (N = 98)	Original OaK Dataset (N = 8,085)
Age in years, mean (SD)	30.1 (5.2)	29.8 (4.6)	31.4 (5.3)	25.7 (10.2)	30.4 (5.7)	30.3 (5.3)
Weight in kg, mean (SD)	96.9 (28.6)	82.3 (22.8)	91.6 (24.8)	60.1 (30.2)	69.4 (22.8)	68.7 (19.9)
Height in cm, mean (SD)	NA	NA	NA	139.2 (59.3)	163.6 (17.3)	163.7 (14.4)
BMI in kg/m^2, mean (SD)	35.6 (9.4)	31.0 (8.6)	34.0 (11.2)	NA	NA	NA
G (gravidity), median (interquartile range)	3 (2 to 4.5)	2 (2 to 3)	2 (2 to 4)	2.8 (2 to 4)	2 (1 to 3)	2 (1 to 3)
T (number of term births), median (interquartile range)	1 (0.5 to 1.5)	1 (0 to 1)	1 (0 to 1)	2 (1 to 2)	0 (0 to 1)	1 (0 to 1)
P (number of preterm births), median (interquartile range)	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)	2 (0 to 2)	0 (0 to 0)	0 (0 to 0)
A (number of abortions/ miscarriage), median (interquartile range)	1 (0 to 1)	0 (0 to 1)	0 (0 to 1)	2 (1 to 2)	0 (0 to 1)	0 (0 to 2)
L (number of living children), median (interquartile range)	2 (1 to 2)	0 (0 to 1)	1 (0 to 1)	2 (1 to 2)	0 (0 to 1)	1 (0 to 1)
M (number of multiple	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	2 (0 – 2)	0 (0 – 0)	0 (0 – 0)

Variable	FACT Isolation Forest Outliers (N = 19)	FACT Random Forest Outliers (N = 13)	Original FACT Dataset (N = 2,301)	OaK Isolation Forest Outliers (N = 172)	OaK Random Forest Outliers (N = 98)	Original OaK Dataset (N = 8,085)
pregnancies), median (interquartile range)						
Current multiple pregnancy, n (%)	7 (36.8)	Suppressed*	428 (18.6)	141 (82.0)	Suppressed*	361 (4.5)
Assisted reproductive technology pregnancy, n (%)	Suppressed*	Suppressed*	213 (9.3)	Suppressed*	Suppressed*	359 (4.4)
History of chronic hypertension, n (%)	7 (36.8)	Suppressed*	423 (18.4)	Suppressed*	0 (0)	101 (1.3)
History of gestational diabetes, n (%)	NA	NA	NA	Suppressed*	Suppressed*	141 (1.7)
History of diabetes mellitus, n(%)	6 (31.6)	Suppressed*	311 (13.5)	NA	NA	NA
History of preeclampsia, n (%)	10 (52.6)	Suppressed*	581 (25.3)	7 (4.1)	Suppressed*	237 (2.9)
History of smoking, n (%)	13 (68.4)	Suppressed*	919 (39.9)	36 (20.9)	9 (9.2)	766 (9.5)
Smoking during pregnancy, n (%)	13 (68.4)	Suppressed*	173 (7.5)	NA	NA	NA
Alcohol use during pregnancy, n (%)	0 (0)	Suppressed*	48 (2.1)	NA	NA	NA
Folic acid supplementation, n (%)	9 (47.4)	11 (84.6)	1,882 (81.8)	43 (25.0)	22 (22.4)	1,786 (22.1)
Aspirin, n (%)	Suppressed*	Suppressed*	665 (28.9)	NA	NA	NA
Calcium supplementation, n (%)	Suppressed*	Suppressed*	196 (8.5)	NA	NA	NA
Other medications, n (%)	14 (73.7)	10 (76.9)	1,620 (70.4)	59 (34.3)	34 (34.7)	2,740 (33.9)
Last systolic blood pressure measurement during pregnancy, mean (SD)	101.9 (72.5)	142.8 (17.3)	136.1 (18.2)	NA	NA	NA
Last diastolic blood pressure measurement during pregnancy, mean (SD)	61.9 (43.3)	82.9 (10.5)	81.5 (13.0)	NA	NA	NA
Gestational age at delivery, mean (SD)	32.8 (5.9)	38.3 (1.9)	37.8 (2.8)	9.9 (7.7)	38.5 (4.4)	38.0 (6.0)

Variable	FACT Isolation Forest Outliers (N = 19)	FACT Random Forest Outliers (N = 13)	Original FACT Dataset (N = 2,301)	OaK Isolation Forest Outliers (N = 172)	OaK Random Forest Outliers (N = 98)	Original OaK Dataset (N = 8,085)
Individuals with preeclampsia, n (%)	8 (42.1)	12 (92.3)	325 (14.1)	Suppressed*	33 (33.7)	249 (3.1)
Individuals with hypertensive disorders of pregnancy, n (%)	NA	NA	NA	Suppressed*	98 (100.0)	597 (7.4)

BMI = body mass index; FACT= Folic Acid Clinical Trial; NA = not applicable; OaK = Ottawa and Kingston Birth Cohort; SD = standard deviation.
* Cells with medical information pertaining to less than seven aggregate participants are suppressed to protect privacy and safeguard participants' data.

We noticed that FACT outliers, compared to the original full dataset, had similar mean age, mean weight, and mean BMI; there was a similarity in the proportion of individuals reporting alcohol use during pregnancy, and the proportion of individuals reporting the use of concomitant medications was also similar. Beyond that, outliers had a higher number of previous pregnancies, more twin pregnancies, and a higher proportion of participants with a history of chronic hypertension, diabetes, eclampsia, and smoking. The FACT outliers were less likely to be on folic acid supplementation or Aspirin and had their delivery at a lower weeks gestation age than the full dataset. The FACT outliers also had lower mean systolic and diastolic measures than the original dataset, but that also came with a larger SD than observed in the original dataset. All of these observations indicate that FACT outliers appear to be at a higher risk of developing preeclampsia, which is reinforced by higher proportions of FACT outliers experiencing preeclampsia than in the original dataset.

The OaK outliers had similar proportions of individuals with a history of chronic hypertension, gestational diabetes, and history of preeclampsia. Also, they were similarly likely to have been on folic acid supplementation or other concomitant medication. They were less likely to develop preeclampsia or hypertensive disorders during pregnancy. The OaK outliers displayed a markedly lower gestational age at delivery than the original dataset.

We also observed that the outliers identified through the isolation forest had a high proportion of lost-to-follow-up cases. Specifically, there were 12 outliers in the FACT outliers that were lost to follow-up (63.2%) compared to an overall 11.3% in the original full dataset. Similarly, there were 85 outliers in the OaK outliers that were lost to follow-up (49.4%) compared to 2.3% overall lost-to-follow-up in the original full dataset.

4.9.3.2 Random Forest

Under the random forest model, 13 outliers (0.6%) were identified in the FACT dataset and 98 outliers (1.2%) in the OaK dataset. We have presented the characteristics of these outliers in contrast to the original datasets in Table 10.

In both datasets, the outliers (identified through the random forest extreme misclassification approach) were of similar age; gravidity, term, preterm, abortion, living; history of chronic hypertension; folic acid supplementation (outside of FACT intervention); and gestational age at delivery as in their original datasets.

The FACT outliers also had a similar proportion of individuals with a history of diabetes, current Aspirin intake, and mean diastolic blood pressure as in the full FACT dataset. The FACT outliers had lower weight and BMI, fewer individuals with multiple pregnancies, fewer pregnancies with assisted reproductive technology, and fewer individuals with a history of smoking. They also had a higher proportion of individuals with a history of preeclampsia, smoking during pregnancy, the use of alcohol during pregnancy, the use of calcium channel blockers, and the use of other medications. Moreover, FACT outliers had higher mean diastolic blood pressure than the original full dataset. The OaK outliers had similar weight, height, history of gestational diabetes, history of preeclampsia, and proportion of participants taking medications.

Under the extreme misclassification approach, FACT and OaK outliers display a much higher proportion of participants with preeclampsia and hypertensive disorders of pregnancy than their full datasets. We also observed that while lost-to-follow-up cases were higher in FACT outliers at two cases (15.4%) than the original dataset (11.3%), this was considerably lower than the proportion of lost-to-follow-up cases in FACT outliers identified through the isolation forest. There were no lost-to-follow-up cases in the OaK outliers.

4.9.4 Assessment of Outliers

Upon review of each outlier observation identified in the FACT dataset, we determined that three outliers (15.8%) in the isolation forest and 10 (76.9%) in the random forest extreme misclassification approaches were potential novelties worthy of further investigation. Similarly, upon review of each outlier observation identified in the OaK dataset, we determined that four outliers (2.3%) in the isolation forest and 32 (32.7%) in the random forest extreme

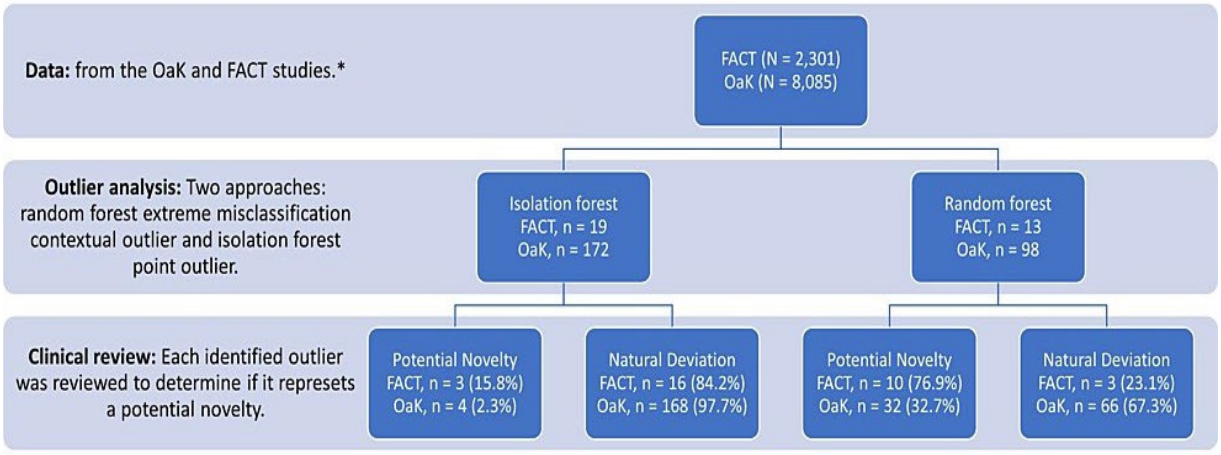
misclassification approaches were potential novelties worthy of further investigation. A summary of our assessment can be found in Table 12. Our findings are further outlined as a flowchart in Figure 5.

Table 12: Detected Outliers and Results of the Assessment of Their Case Narratives

Model	FACT	OaK
Isolation forest		
Total outliers identified, n	19	172
Outliers determined as potential novelty, n (%)	3 (15.8)	4 (2.3)
Outliers determined as natural deviation, n (%)	16 (84.2)	168 (97.7)
Random forest extreme misclassification		
Total outliers identified, n	13	98
Outliers determined as potential novelty, n (%)	10 (76.9)	32 (32.7)
Outliers determined as natural deviation, n (%)	3 (23.1)	66 (67.3)

FACT = Folic Acid Clinical Trial; OaK = Ottawa and Kingston Birth Cohort.

Figure 5: Flowchart of Results Per Analysis Stage



FACT = Folic Acid Clinical Trial; OaK = Ottawa and Kingston Birth Cohort. * Data from each study were analyzed separately and were not combined.

4.10 Discussion

In this study, we demonstrated the feasibility of applying an augmented intelligence outlier analysis framework on clinical trials and real-world data. This approach could accelerate the rate of clinical discovery that has traditionally depended on the observation and research skills of individual clinicians. Although the use of outlier analysis for uncovering new clinical insights was first proposed in a publication in 2000 by Laurikkala et al.,[47] to the best of our efforts, we

were unable to find published studies approaching this problem from a contextual outlier analysis perspective using extreme misclassification of a random forest model.

Out of 2,301 participants in the FACT study, we identified 19 outliers using the isolation forest algorithm and 13 outliers using the random forest extreme misclassification approach. Of these, a clinical review determined that three (15.8%) and 10 (76.9%) were potential novelties in the isolation forest and random forest extreme misclassification approaches, respectively, warranting further investigation through source documents review and participant follow-up. Out of 8,085 participants in the OaK study, we identified 172 outliers using the isolation forest algorithm and 98 outliers using the random forest extreme misclassification approach; four (2.3%) and 32 (32.7%), respectively, were potential novelties worthy of further investigation.

In both FACT and OaK datasets, there were more potential novelties within the outliers identified through the random forest extreme misclassification approach (FACT 76.9%, OaK 32.7%) than through the isolation forest approach (FACT 15.8%, OaK 2.3%). Several observations can be made from these results. First, our contextual outlier analysis approach using extreme misclassification has captured a higher number and proportion of potential novelties compared to a standard outlier approach using isolation forest in both datasets. This indicates the advantage of the contextual outlier approach using extreme misclassification. Despite capturing a lesser total number of outliers, it still managed to produce a higher number of potential novelties. This can also be explained by the tendency of the isolation forest algorithm to identify observations that are the easiest to isolate, which manifested in capturing cases that were lost-to-follow-up, withdrew from the study, or experienced early termination. These cases had little information to allow the clinical review to determine if there were any potential novelties.

A second observation was that regardless of the model, we noticed an overall higher proportion of potential novelties in FACT outliers than in OaK outliers. This may be due to the structure and type of variables (features) of the underlying data. For example, the FACT study collected several blood pressure measurements as well as laboratory tests throughout the trial. In contrast, no similar longitudinal variables were collected in the OaK study. This observation is likely to inform future expectations of the proportion of outliers and novelties within datasets based on the dataset design and structure. It is important to note that only one observation within the OaK dataset was identified by both outlier methods; the remaining were unique to each approach.

Similarly, all outlier observations within the FACT dataset were unique to each approach with no overlap. This could be explained by the inherently different assumptions and definitions of outliers in each model, whereby the isolation forest depends on unique values in the features. In contrast, the extreme misclassification approach depends on the poor fit of an observation to an outcome classification model.

Based on the results obtained in this study, we believe that the extreme misclassification approach is likely to perform better on both real-world data and clinical trial data. However, considering our previous observation of the minimum overlap in outliers between the two approaches, it is possible that there is room for both approaches to work in parallel to maximize the number of identified potential novelties.

Across all of the datasets and approaches, our clinical review identified 49 observations as potential novelties based on the case narratives of these observations. Ideally, the next step would be to investigate source documentation and potentially follow up with these participants to understand better if an unrecorded factor may have contributed to the unusual clinical observations. Based on the unstructured notes that were added throughout the clinical review of each outlier, there seems to be a common theme supporting further investigation of the potential role of recorded and unrecorded concomitant medications in contributing to the nature of the observations. Moreover, another theme emerged that indicated that there is room to reassess the traditional importance of certain risk factors when they are simultaneously present with concomitant medication. Both themes can serve as the basis for investigating novelties and formulating scientific hypotheses.

There were several limitations in our study. These include the lack of blinding of the clinical reviewers to the type of model that identified the outlier being assessed. This could have biased the determination of potential novelties in favour of the new approach of extreme misclassification. Blinding the clinical reviewers was not feasible as they needed the model information insight to better understand why a given observation is identified as an outlier. Another important limitation was the lack of a final assessment of the performance of these outlier models in identifying true novel cases that could lead to a clinical discovery. This final assessment can only occur after the determined potential novelties are investigated further through source document review and participants' follow-up, which we were unable to do in this

study. Another potential limitation was that the actual outcome for the classification model in both datasets was relatively low (14.1% in FACT and 7.4% in OaK), which may have caused an imbalanced classification, leading to poor recall of the random forest model in both datasets. Within the extreme misclassification approach, the poor recall meant that there was a higher proportion of outliers that were misclassified as not having the outcome compared to outliers that were misclassified as having the outcome. It is also important to note that the classification model is not meant to act as a clinical prediction model and included variables such as the fetal Apgar score, gestational age at delivery, blood pressure measurements, and laboratory results that would not be useful for the development of a clinical prediction model. Finally, it is important to note that the generalizability of the finding is that extreme misclassification performs better than isolation forest and may be limited considering the use of two studies, both of which are in the field of obstetrics.

4.11 Conclusions

Unique and unusual clinical observations have been the catalyst for clinical discovery. An efficient way is needed to identify and pursue such observations. In this study, we demonstrated the feasibility, applicability, and potential benefits of utilizing augmented intelligence outlier analysis methods to accelerate the rate of clinical discovery, particularly in preeclampsia and hypertensive disorders of pregnancy. Furthermore, we applied our proposed extreme misclassification contextual outlier analysis approach to real-world and clinical trial data by using the datasets from the FACT and OaK studies as test cases. Our results have shown a higher proportion of potential novelties under the extreme misclassification approach compared to the isolation forest approach in both the clinical trial and real-world data. Our findings suggest that an extreme misclassification contextual outlier approach may have advantages over the classical point outlier analysis approach in identifying cases with potential novelty and thus accelerating the rate of clinical discovery. The application of augmented intelligence using outlier analysis to accelerate the rate of clinical discovery can be implemented in various clinical disciplines and utilized within electronic medical records to identify outliers to clinical experts automatically.

4.12 Additional Information

4.12.1 Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Ottawa Health Science Network Research Ethics Board issued approval 20220109-01H. This study received ethics approval from the Ottawa Health Science Network Research Ethics Board. Certificate ID 3589 was issued for protocol ID 20220109-01H. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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5 CHAPTER 5: THESIS DISCUSSION AND CONCLUSION

What is discovery? This question is at the heart of the philosophy of science. The concept of scientific discovery and whether there is a particular method that leads to discoveries is one that epistemologists and scientists have fiercely debated. The prevailing thinking in the 17th century was that following a prescribed method of inquiry would inevitably lead to discovery. Such thinking was formulated and popularized by Francis Bacon, René Descartes, Isaac Newton, and many of their contemporaries. Their inquiry methods and approaches were thought to lead not only to discoveries that should be investigated further but to actual intellectual truths. And they were justified as the truth because they were generated through prescribed methods of inquiry.

The 19th century witnessed a considerable decline in the classic traditions of inquiry methods leading to discoveries. This decline was fuelled by Romanticism ― the late 18th century movement that popularized the "aha" or moment of creativity (i.e., inspiration) ― and by the failure of many of these models of inquiry methods to produce and sustain scientific advancements. Advancements in mathematical work on approximation and statistical inferences have also led to a more dynamic and iterative understanding of the scientific method. These factors have culminated into what is the currently prevailing scientific method, the hypothetico-deductive model, whereby a hypothesis is postulated in a falsifiable manner and then tested by inducing or inferring outcomes. In such an approach, how or why the hypothesis originated is of little importance.[92]

Clinical research closely follows the hypothetico-deductive model, as evident by the keen, almost universal adoption of the hierarchy pyramid of evidence. While there have been many variations to the pyramid, a common theme is emphasizing comparative research design, mainly randomized controlled trials.[93] However, potentially unique to the field of clinical scientific research, clinical equipoise has always been an essential part of the ethical conduct of clinical research, placing emphasis and importance on how or why a hypothesis originated in the first place.[94] As a result of the high ethical standards needed to ensure that patients' safety and rights are protected, descriptive research, including case reports and case series, has always found a place in the hierarchy of evidence. We would be remiss to neglect the increasing adoption of Bayesian statistics and Bayesian thinking as indications that "how the hypothesis came to be" is becoming an increasingly important part of the scientific method within clinical research.[95]

In this thesis, our goal was relatively simple: Could we find a way to increase the rate of clinical discoveries? We did not delve much into the epistemology of clinical discovery, nor did we postulate establishing an inquiry method that would lead to an unfalsifiable intellectual truth in the style of the 17th century. We assumed that the more clinical discoveries we could find, the more hypotheses we could test, and the faster we would find therapies. To that aim, we chose preeclampsia and other hypertensive disorders of pregnancy as appropriate targets because of the significant and large public unmet need for clinical discovery in this area and the lack of industry-sponsored research. We then looked to other research fields for inspiration on how to approach the problem of knowledge discovery, which led us to propose using outlier analysis as a potential promising study design. Our understanding of the clinical human-based process of identifying unique individual patients for further investigation has led us to propose the extreme misclassification contextual outlier algorithm in conjunction with subject-matter expert reviews within an augmented intelligence framework. With these various pieces, we sought to understand what clinical discovery in preeclampsia looks like, how outlier analysis is used in obstetrics research, and whether our proposed approach would identify promising observations.

5.1 Summary of Findings

In our systematic review and assessment of preeclampsia case reports and case series, we discovered that just under a quarter of these (24.3%) had a novel clinical discovery component. We also found that just 8% of these were of high quality, as assessed through the JBI critical appraisal checklist for case reports and case series. These surprising findings suggest that the traditional approach to clinical discovery through communicating novel findings in case reports and case series needs further development and evolution.

We suggest that a way to move forward in increasing the efficiencies in clinical discoveries based on individual patient observations would be through outlier analysis within an augmented intelligence framework. Furthermore, we propose a novel approach within outlier analysis that would mimic the traditional clinical process of identifying unique clinical observations. To summarize, the framework consisted of five steps: 1) defining a patient population and a clinical outcome; 2) developing a predictive model of the patient population; 3) defining outlier measures; 4) reviewing identified outliers by a subject-matter expert; and, finally, 5) formulating a scientific hypothesis based on the outliers that were determined as potential clinical discoveries

by the subject-matter expert. Considering the use of outlier analysis, we also wanted to explore how outlier analysis is being used within obstetrics research. To answer that question, we conducted a systematic review of outlier analysis in obstetrics research. We were only able to find two published papers that used outlier analysis methods for identifying teen pregnancy rates in US counties and another to identify obstetric care outside of the Ministry of Health recommendation in Italy.

We put our framework into action by applying it to two datasets: data from FACT and data from the OaK Birth Cohort. These two datasets were chosen to represent the highly controlled data from a clinical trial (i.e., FACT) and the more general data that can represent real-world settings (i.e., OaK). We also further detailed our novel predictive model-based approach to outlier analysis by introducing, implementing, and comparing the extreme misclassification contextual outlier algorithm against a more traditional point outlier approach of isolation forest.

The results suggested that our framework uncovered observations in both datasets of potential clinical discovery value that have not been identified before ― a total of 13 potential novel observations in FACT (0.6%) and 36 potential novel observations in OaK (0.4%) across both outlier analysis methods. We also reported that our proposed outlier analysis approach of extreme misclassification contextual outlier performed numerically better than the classic isolation forest point outlier approach in identifying potential novel observations. Furthermore, based on the case narratives of the identified potential novelties, there appears to be a recurring pattern that suggests a need for further investigation into the possible impact of both recorded and unrecorded concomitant medications on the nature of the observations. Another pattern emerged, indicating a need to reconsider the conventional significance of specific risk factors when they are present concurrently with concomitant medication. These two themes could provide a foundation for exploring new ideas and developing scientific hypotheses.

5.2 Strengths and Limitations

5.2.1 Strengths

This thesis proposed and implemented a novel augmented intelligence framework and outlier analysis method to screen large amounts of medical data and flag unique observations for additional review by a subject-matter expert. This novel contribution is further augmented by

addressing several knowledge gaps regarding the contribution of case reports and case series to clinical discovery in preeclampsia and the use of outlier analysis methods in obstetrics.

A major strength of this thesis is the use of two different datasets that allowed the representation of real-world data, as well as data from the controlled settings of clinical trials. Another important strength is the active comparison of the proposed extreme misclassification contextual outlier analysis method with the commonly utilized isolation forest point outlier analysis method. The use of an augmented intelligence framework has allowed the refinement of our observations from a general state of "outliers" to the more specific and desired state of "potential novelties" without the need to acquire a large quantity of labelled data to train a traditional supervised classification model for identifying potential novelties. Finally, we conducted systematic reviews to address the knowledge gaps related to this thesis.

5.2.2 Limitations

Implementation of our augmented intelligence framework has resulted in identifying a total of 0.6% of the observations in the FACT dataset and 0.4% of the observations in the OaK dataset as potentially representing clinical novelties. It is tempting to draw a conclusion that augmented intelligence using outlier analysis would identify 0.4% to 0.6% of potential novelties in any dataset. However, this would be generalizing the results of what is effectively a sample of n = 2. It would, therefore, be inappropriate to generalize results from such a small sample size. Our findings do, however, support the feasibility and applicability of applying the proposed framework to identify previously uninvestigated clinical cases that are potential novelties.

Generalizability limitations extend to our systematic reviews to address the evidence gaps in the clinical discovery and outlier analysis fields. Our systematic review of case reports and case series was restricted to English publications, to the field of preeclampsia, and to five years between 2015 to 2020. We believe that the publication period has no significant impact on the generalizability of the results. Unlike the relatively small sample size in our framework application and comparison, the systematic review of case reports and case series included a total of 104 case reports and case series. Moreover, the result of the systematic review is not that of synthesizing evidence of the efficacy and safety of treatment from results within the included articles. Such synthesis is susceptible to significant change should a new study with a large sample size appear. Instead, our sample was the included studies themselves as opposed to the

patients within these studies. Our assessment was that of the contribution of each included study to clinical discovery in preeclampsia. Therefore, it is unlikely that newly published case reports and case series would significantly impact the results. That being said, the fact that we only addressed preeclampsia-related case reports and case series is likely to limit the generalizability of the results to the field of preeclampsia research.

A limitation of this thesis was our inability to publish the case narratives of the identified outliers and potential novelties. This restriction on publishing case narratives is to protect and safeguard the privacy and identity of patients as per the obtained ethics approval. Future research should incorporate appropriate risk measures and obtain all necessary permissions to conduct and communicate the analysis of the available information on the potential outliers.

The choice and definition of various terms used in this thesis have proved challenging to harmonize. This challenge is mainly caused by the interdisciplinary nature of the thesis, whereby several fields of study intersect. These fields include but are not limited to epidemiology, clinical obstetrics, statistics, and machine learning. For concepts and items that clearly originated from a specific field (e.g., description of FACT and OaK datasets as per clinical epidemiology terminology), we have attempted to use the appropriate terms most closely associated with the originating field.

Finally, the lack of follow-up on the identified potential novelties is also a limitation of this study. When implementing our augmented framework and reviewing the identified outliers, we adopted a practical approach of a “diagnosis of exclusion” for assessing whether an outlier represented a potential novelty. In essence, if the reviewer could not explain, within a reasonable level of certainty, how the observed outcome in each outlier came to be, that outcome would have qualified for the label of a potential novelty. Ideally, identifying such potential novelties would then lead to further investigation through source document reviews and potential follow-ups with patients. The follow-ups would aim to further elicit and document information to either explain the observation or to identify potential factors that may have influenced the observed outcome. Such follow-ups were not feasible and not necessary for addressing the core objectives of this thesis.

5.3 Practice Implications and Future Research

Serendipity is "the gift of finding valuable or agreeable things not looked for," according to the *Merriam-Webster* dictionary.[96] Serendipity implies an unexpected and uncontrollable event that one did not plan or work towards. In other dictionaries, there is an emphasis on the chance or accidental aspect of this positive and valuable occurence.[97,98] The most significant implication this thesis can have on clinical practice is to turn the accidental aspect of "serendipity" in clinical research into a measurable and calculated outcome.

In the current state, the clinical discovery process is almost entirely human-driven. It depends on busy clinicians and healthcare professionals' keen observations and scholarly initiatives. Expecting these busy healthcare professionals to review every patient record for potential novel clinical insights is also unrealistic. Undoubtedly, many possible clinical discoveries have been missed under the current process. Applying our proposed augmented intelligence framework would allow the screening of many patient records, identifying the most unusual ones for further review by a subject-matter expert. Thus, this approach would ensure that every patient entry has been assessed for potential unique and unusual clinical insight. Should this framework be implemented on a broad scale, it may increase the rate at which new insights and knowledge of disease and therapeutics are produced.

This thesis also provides important contributions in addressing knowledge gaps related to clinical discovery in preeclampsia. Despite classical assumptions around case reports and case series, we have shown that the majority of these case reports and case series did not claim to communicate a novel clinical insight into preeclampsia. We also demonstrated that the quality of published case reports and case series in preeclampsia is low to moderate. We have provided general recommendations on how the quality of case reports and case series can be improved to allow the use of this vital study design to generate and test new hypotheses. Applying these recommendations would allow the potential use of case reports and case series as valuable sources of individual patient data.

Future research in this field would include the application of the augmented intelligence framework on administrative databases and electronic medical records, applying the framework to other disease areas, and conducting follow-up studies for patients whose records were identified as a potential novelty. In an ideal world, we envision a dedicated group of researchers

that would build the outlier analysis models, maintain the data flow into these models, engage subject-matter experts on identified outliers, and follow up on patients. Such a group would aim to formulate novel clinical hypotheses based on the patterns, insights, and unusual factors uncovered in the augmented intelligence framework.

5.4 Conclusion

In this thesis, we addressed the knowledge gaps in clinical case reports and case series in preeclampsia in their collective role of advancing our knowledge of the disease through clinical discoveries. We also addressed the knowledge gap of how outlier analysis methods are used in obstetrics research. Through an augmented intelligence framework, we proposed a novel approach in outlier analysis combined with the judgment of human reviews to identify unique clinical observations that can lead to clinical discoveries. We then applied the proposed framework to two different datasets of pregnant individuals to identify unique observations that could advance our understanding of preeclampsia and other hypertensive disorders of pregnancy.

Based on this approach, we identified several observations that were potential novelties. This finding indicates the feasibility and applicability of our proposed augmented intelligence framework in identifying previously uninvestigated clinical cases with the potential for new clinical insights. Applying such an augmented intelligence framework to various medical data ― including administrative databases and electronic medical records ― could fuel and accelerate the rate of new clinical discoveries in a more focused and less haphazard manner.

6 CHAPTER 6: REFERENCES

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7 CHAPTER 7: APPENDICES

7.1 Appendix 1: Ethics Approval

The Ottawa Hospital | L'Hôpital d'Ottawa
RESEARCH INSTITUTE | INSTITUT DE RECHERCHE

March 01, 2022

Dr. Mark Walker

Attn: Ruth Rennicks White
Ottawa Hospital - General Campus
Department of Obstetrics/Gynecology/Newborn Care
Center for Practice-Changing Research, Room
L1241, Box 241 501 Smyth Road, Ottawa, ON K1H
8L6

Re: OHRI Institutional Approval for Ottawa Health Science Network Research Ethics Board (OHSN-REB) Submission

Protocol ID#: 20220109-01H;

Outlier Analysis for Clinical Discovery: Application in Hypertensive Disorders of Pregnancy Using the Oak Cohort and FACT Studies' Data

Dear Dr. Mark Walker,

This letter serves as **Ottawa Hospital Research Institute (OHRI)** Institutional Approval for the above-referenced study. Please maintain this documentation in your investigator study file.

Based on the information you provided about this study through the Clinical Research Registration Form, you have satisfied the requirements for institutional (OHRI) approval. This includes initial research ethics approval by OHSN- REB, appropriate departmental/service area notifications and execution (fully signed versions) of all agreement(s) required to begin the study locally. Please note there may be additional agreement(s) pending execution that are required to send funds, samples, or data to external sites, but are not required for you to begin your study locally.

Changes and/or additions to your study that may require additional agreement(s) or revisions to existing agreement(s) must be communicated to the OHRI Contracts Office. This should be undertaken simultaneously with any related OHSN-REB amendment submission.

Changes and/or additions to your study that affect various hospital/institution departments (e.g., pharmacy, Department of Medical Imaging, EORLA, EEG, etc.) must be communicated to the relevant departments.

As mentioned in the 'Response' tab of the Ethics application, you have 3 months from the date of initial OHSN-REB approval to submit French documents including the translation certificate to OHSN-REB through the Translated Documents section of the ethics application (if applicable).

Should you have any questions, please contact REBadministration@ohri.ca or 613-798-5555 extension 16719.

Ottawa Hospital Research Institute | Institut de recherche de l'Hôpital d'Ottawa

Civic Campus, Box 675, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9 613-798-5555 extension 16719 Fax : 613-761-4311 http://www.ohri.ca/ohsn-reb

7.2 Appendix 2: Published Version of First Component Article

REVIEW

Do Case Reports and Case Series Generate Clinical Discoveries About Preeclampsia? A Systematic Review

Authors Janoudi G, Uzun (Rada) M, Boyd ST, Fell DB, Ray JG, Foster AM, Giffen R, Clifford TJ, Walker MC

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Ghayath Janoudi,[1,2] Mara Uzun (Rada),[3] Stephanie T Boyd,[1] Deshayne B Fell,[2,4] Joel G Ray,[5] Angel M Foster,[6] Randy Giffen,[7] Tammy J Clifford,[2,8] Mark C Walker[1,2,9–12]

[1]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada; [2]School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada; [3]Independent Researcher, Ottawa, ON, Canada; [4]Children's Hospital of Eastern Ontario (CHEO) Research Institute, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada; [5]Departments of Medicine, Health Policy Management and Evaluation, and Obstetrics and Gynecology, St Michael's Hospital, University of Toronto, Toronto, ON, Canada; [6]Faculty of Health Sciences, University of Ottawa, Ottawa, ON, Canada; [7]IBM Canada, IBM, Toronto, ON, Canada; [8]Canadian Institute of Health Research, Government of Canada, Ottawa, ON, Canada; [9]International and Global Health Office, University of Ottawa, Ottawa, ON, Canada; [10]Department of Obstetrics and Gynecology, University of Ottawa, Ottawa, ON, Canada; [11]Department of Obstetrics, Gynecology & Newborn Care, The Ottawa Hospital, Ottawa, ON, Canada; [12]BORN Ontario, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

Correspondence: Mark C Walker, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Centre for Practice Changing Research, Box 241, 501 Smyth Road, Ottawa, ON, K1H 8L6, Canada, Tel +1 613-798-5555 x76655, Email mwalker@toh.ca

Background: Preeclampsia is a leading cause of maternal and perinatal mortality and morbidity. The management of preeclampsia has not changed much in more than two decades, and its aetiology is still not fully understood. Case reports and case series have traditionally been used to communicate new knowledge about existing conditions. Whether this is true for preeclampsia is not known.

Background: Preeclampsia is a leading cause of maternal and perinatal mortality and morbidity. The management of preeclampsia has not changed much in more than two decades, and its aetiology is still not fully understood. Case reports and case series have traditionally been used to communicate new knowledge about existing conditions. Whether this is true for preeclampsia is not known.
Objective: To determine whether recent case reports or case series have generated new knowledge and clinical discoveries about preeclampsia.
Methods: A detailed search strategy was developed in consultation with a medical librarian. Two bibliographic databases were searched through Ovid: Embase and MEDLINE. We selected case reports or case series published between 2015 and 2020, comprising pregnant persons diagnosed with hypertensive disorders of pregnancy, including preeclampsia. Two reviewers independently screened all publications. One reviewer extracted data from included studies, while another conducted a quality check of extracted data. We developed a codebook to guide our data extraction and outcomes assessment. The quality of each report was determined based on Joanna Briggs Institute (JBI) critical appraisal checklist for case reports and case series.
Results: We included 104 case reports and three case series, together comprising 118 pregnancies. A severe presentation or complication of preeclampsia was reported in 81% of pregnancies, and 84% had a positive maternal outcome, free of death or persistent complications. Only 8% of the case reports were deemed to be of high quality, and 53.8% of moderate quality; none of the case series were of high quality. A total of 26 of the 107 publications (24.3%) included a novel clinical discovery as a central theme.
Conclusion: Over two-thirds of recent case reports and case series about preeclampsia do not appear to present new knowledge or discoveries about preeclampsia, and most are of low quality.

Keywords: hypertensive disorders of pregnancy, eclampsia, HELLP syndrome, study design

Introduction

Knowledge of diseases, therapeutics, and the human body has been largely gained through the accumulation of clinical observations.[1–3] Meticulous observation is the cornerstone of clinical research, and scientific research in general.[2–5] Traditionally, case reports and case series have been utilized as a medium to communicate these preliminary clinical observations and discoveries.[6–8] These descriptive observational studies serve to generate scientific hypotheses that can then be tested further in comparative study designs.[9] Many medical discoveries have first been reported in the literature as case reports or case series. Several examples include lithium's and chlorpromazine's psychopharmacological properties,[10–12] malignant hyperthermia with dantrolene as its treatment,[13,14] toxic shock syndrome and its association with tampon use,[15,16] and the description of rare forms of infections and malignancies leading to the discovery of HIV infection.[17,18] Most recently, we have witnessed the use of individual clinical observations, communicated in various formats, in the detection and management of COVID-19.[19–23]

In antiquity, case reports were the main vehicles that physicians used to convey disease descriptions, treatments, and pass teachings.[24] The 20th century heralded large advancements in clinical study design and generated a strong debate on the role of case reports and case series. This culminated in the adoption of the evidence-based medicine hierarchy in the 90s that relegated case reports and case series to the bottom of the clinical evidence pyramid.[7] Many peer review journals no longer publish case reports. On the other hand, several journals have emerged that are specialized in publishing case reports and case series.[7,25] Despite being considered at the bottom of the clinical evidence hierarchy, case reports and case series are an integral part of evidence-based medicine practices.[26] This is why in 2014, a working group of researchers and methodologist was formed within The Joanna Briggs Institute (JBI), an international not-for-profit organization that aims to improve the quality of health care through evidence-based practices, to establish critical appraisal tools for case reports and case series.[27]

The hypertensive disorders of pregnancy are a leading cause of maternal mortality and morbidity worldwide,[28] and are responsible for approximately 18% of all maternal deaths globally and affect an estimated 5% to 10% of all pregnancies.[29–33] Preeclampsia is one such hypertensive disorder of pregnancy — a pregnancy complication characterized by resistant hypertension with proteinuria or with other adverse conditions or complications.[34] Severe forms of preeclampsia can manifest as hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome and untreated preeclampsia can lead to eclampsia.[35] Both HELLP and eclampsia are associated with a high degree of morbidity and mortality.[36–38] Hypertensive disorders of pregnancy and their associated complications are some of the oldest-ever recorded medical conditions; one of the first descriptions of eclampsia was recorded by Hippocrates in the 5th century BCE.[39] Understanding of the pathophysiology of hypertensive disorders of pregnancy has grown since and has advanced considerably in the past two decades, yet the clinical management of preeclampsia has not changed much.[40–46] Similarly, preventive approaches to preeclampsia have mostly fallen short, with the exception of the use of aspirin for the prevention of early severe preeclampsia.[47–49]

Considering the traditional role of case reports and case studies in medicine as a vehicle to communicate new clinical discoveries, we aimed to assess the extent to which recent case reports and case series have communicated clinical discoveries that have advanced our knowledge of preeclampsia through a systematic review. Systematic reviews in case reports and case series are common in the literature and traditionally aim to synthesize and assess rare clinical

preventive approaches to preeclampsia have mostly fallen short, with the exception of the use of aspirin for the prevention of early severe preeclampsia.[47–49]

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Methods

We registered this study as a systematic review protocol on the international prospective register of systematic reviews (PROSPERO) under ID number CRD42020209953, with the outlined methods that follow. We added one amendment to the protocol to further clarify exclusion criteria and to define additional terms.

Search Strategy

We developed a detailed search strategy to identify case reports and case series on hypertensive disorders of pregnancy. The search strategy was developed in consultation with a medical information specialist (see Appendix S1) and consisted of controlled vocabulary, as well as keywords. The main search concepts were hypertensive disorders of pregnancy and case reports/case series. We searched two main bibliographic databases: Ovid Embase and Ovid MEDLINE. The search strategy filtered the results for human studies and the English language. Subsequently, we retrieved studies published between 2015 and 2020 for screening. We conducted the search strategy on August 3, 2020, and did not conduct any additional searches or establish alerts.

Study Selection

This systematic review includes case reports or case series in pregnant persons diagnosed with hypertensive disorders of pregnancy. We outline the specific eligibility criteria in Table 1.

Table 1 Inclusion and Exclusion Criteria for the Systematic Review

Two independent reviewers screened all retrieved records in two stages: title and abstract screening (GJ and SB) and full-text screening (GJ and MU). We resolved rare disagreements through discussion; if we were unable to reach an agreement, we engaged a third independent reviewer (MW) as arbiter.

Data Extraction and Synthesis

The overall data extraction and synthesis process followed a content analysis approach. Upon completion of article selection, we used a random sample of 10 articles to develop a codebook to establish the required data extraction fields, as well as definitions of outcome categories. We used an additional random sample of 10 articles to further refine the codebook, as well as the data extraction sheet. After finalizing the codebook and extraction sheet, GJ performed all extraction and abstraction activities. MU then conducted a data quality check on at least 20% of the extracted data.

For each included article, GJ extracted all data that were relevant to the study design characteristics, patients' baseline and demographic characteristics, intervention/exposure characteristics, and outcome characteristics.

Based on the information presented within the full text of each included article, GJ determined the severity of each patient's presentation or complication, the novelty of the exposure that the patient was reported to have experienced, whether the outcome was positive or negative, the reason for publishing the study, and whether a scientific hypothesis as a result of an observation was reported. We provide the definitions of these categories in Table 2.

Table 2 Outcome Categories, Category Classification, and Associated Definitions

We provided a descriptive summary of the number of case reports and case series within various categories and classifications. Additionally, we provided a narrative summary of case reports and case series that were determined to have a clinical discovery component. Data collected and used for this review, the codebook, and the extraction sheet are available from the corresponding author upon request.

Quality Assessment

One reviewer (GJ) assessed the quality of the included case reports and case series according to the Joanna Briggs Institute (JBI) critical appraisal Checklist for Case Reports and the JBI critical appraisal Checklist for Case Series.[53] The tool consists of eight questions for case reports and 10 questions for case series that are related to the existence or absence of various reported items. We deemed articles with reported items that addressed more than two-thirds of the

In assessing the publication reasons for the articles we studied, we determined that, of the 107 included articles, 65 (61%) were published as educational material and 26 (24%) as discovery articles; we were unable to determine a clear publication reason for 16 (15%) articles. We present a further breakdown of each classification in Table 3. Of the included studies with a clinical discovery aspect, the following interventions were considered notable ones in the assessment of the reviewers: sildenafil administration in a patient with periviable pregnancy and preeclampsia;[70] selective fetal reduction in cases of discordance in dichorionic twin gestations in patients with preeclampsia or HELLP syndrome;[87,92] continuous positive airway pressure in patients with obesity, obstructive sleep apnea, preeclampsia, and a high risk of developing severe preeclampsia;[107,159] acupuncture therapy in a patient with preeclampsia;[109] plasma exchange therapy for patients with HELLP syndrome;[121,132] eculizumab in a patient with HELLP syndrome;[117] eplerenone in a patient with obesity, obstructive sleep apnea, and preeclampsia;[129] pravastatin in a patient with HELLP syndrome;[137] and dydrogesterone to prevent preeclampsia in a patient with a history of recurrent preeclampsia.[150]

Table 3 Outline of the Results

Authors of the included articles have clearly stated an observation-based scientific hypothesis in nine articles (8%), and we determined that there was an implied scientific hypothesis in 22 articles (21%). Based on our assessment criteria, we determined that the majority of articles (n = 73; 68%) did not include a clearly stated or implied scientific hypothesis. Finally, we were unable to make a determination in three cases (3%). We include a list of the studies that we determined to have reported a clear or implied hypothesis in Appendix S4.

Discussion

Main Findings

To our knowledge and best efforts, we were unable to find a previously published systematic review of case reports and case studies in patients with hypertensive disorders of pregnancy, including preeclampsia. Moreover, we were unable to find published peer-review articles that assessed the extent of clinical discovery contribution of case reports and case series in the field of preeclampsia. Over the period from 2015 to 2020, we identified a total of 104 case reports and three case series reporting on a total of 118 pregnant persons with a diagnosis related to hypertension disorders of pregnancy. Notably, we observed that there is tendency among the included articles to report on patients with severe presentation or complication (81%) and positive maternal outcomes (84%). Indeed, 96 of the 118 patients (81%) that were included in these articles had both a severe presentation or complication and a positive maternal outcome. Further, a sizable majority (61%) of identified manuscripts appeared to be published for educational purposes rather than clinical discovery. We assessed that less than one-third of the included articles were published to communicate a potential clinical discovery (24%).

Interpretation

Case reports and case series can be an important part of the scientific discovery journey by communicating novel clinical observations in a structured and comprehensive manner. Our findings suggest that less than one-quarter of these studies in preeclampsia included a clinical discovery component. This begs the question of how today's novel clinical observations are being communicated with the larger scientific and clinical communities. Moreover, the tendency in reporting severe presentations and complications, coupled with positive maternal outcome, suggests that these case reports and case series are unlikely to be a representative sample of the population.

An important finding is the overall low adherence of the included case reports and case series to established reporting guidelines. Most pronounced was the lack of sufficient reporting on patients' characteristics, important measurements of the clinical condition (eg, laboratory results), type of interventions, and post-intervention status. The lack of such information drastically reduces the educational and clinical discovery value of these articles. Ideally, authors should provide sufficient information on all aspects of the clinical encounter with the patients so as to allow clinicians and researchers to understand and potentially replicate or capture the population, intervention, and outcome in future studies. Authors should note any missing information relevant to the disease of which the case report is describing (eg, blood pressure measurement in preeclampsia). Peer-review journals should ideally ensure that case reports and case series are as comprehensively reported as any other form of clinical study design, reporting on patients' characteristics so

Quality Assessment

One reviewer (GJ) assessed the quality of the included case reports and case series according to the Joanna Briggs Institute (JBI) critical appraisal Checklist for Case Reports and the JBI critical appraisal Checklist for Case Series.[53] The tool consists of eight questions for case reports and 10 questions for case series that are related to the existence or absence of various reported items. We deemed articles with reported items that addressed more than two-thirds of the JBI checklist to be high quality. More than one-third was deemed moderate quality, and less than one-third was deemed to be low quality.

Results

We retrieved a total of 3415 citations from the search strategy. After level 1 title and abstract screening, we selected 303 citations for level 2 full-text screening. After level 2 screening, we included 107 articles in this systematic review.[54–160] We provide a flow chart of included and excluded articles in Figure 1.

Figure 1 Flowchart of included and excluded studies.

Of the 107 included publications, three were case series[105,136,148] and the remainder were case reports. Authors reported on a total of 118 patients in these studies. Our quality assessment of the 104 case reports found that eight reports (8%) were high quality, 56 reports (54%) were moderate quality, and 40 reports (38%) were low quality. We found that the majority of the included case reports addressed two items on the JBI critical appraisal checklist for case reports: the description and presentation of a patient's history as a timeline (97% addressed this item), and the availability of take-away lessons (93% addressed this item). However, we found that only 17% of the included case reports provided sufficient description of a patient's demographic characteristics, which is the first item on the JBI checklist. Furthermore, only one-third of the included case reports provided sufficient description of the intervention (30%) and the post-intervention clinical condition (33%). A detailed description of the quality assessment of each included case report is available in Appendix S2.

We considered two of the three case series to be of low quality and one of moderate quality. All of the included case series described valid methods of identifying the condition of interest and two provided sufficient description on appropriate statistical methods used in the case series. A detailed description of the quality assessment of each included case report is available in Appendix S3.

In the included studies, maternal age and gestational age at first presentation were available for 115 patients, with a mean maternal age of 30.1 years (standard deviation [SD]=6.6) and a mean gestational age of 29.7 weeks' gestation (SD = 6.5). Authors reported information on gravidity for 90 patients: 42 (47%) were primigravida. Authors included a clear presentation complaint for 108 patients; the most common reported symptom on presentation was abdominal pain (n = 33; 31%), followed by headaches (n = 26; 24%). On presentation, the mean systolic blood pressure reported in 92 patients was 163.1 mm Hg (SD = 27.5), while the mean diastolic blood pressure reported in 91 patients was 103.2 mm Hg (SD = 20.0). Authors only sporadically reported on other baseline characteristics, including body mass index, blood laboratory results, urinary laboratory results, liver function tests, and kidney function tests.

The most commonly reported hypertensive disorders of pregnancy diagnoses were preeclampsia (n = 98; 83%), HELLP (n = 40; 34%), hepatic hematoma — including rupture and infarction (n = 16; 14%), eclampsia (n = 10; 9%), and peripartum cardiomyopathy (n = 6; 5%). The most commonly reported interventions were magnesium sulphate (n = 46; 39%), labetalol (n = 15; 13%), hydralazine (n = 13; 11%), and nifedipine (n = 13; 11%). The authors reported that caesarean section was the method of delivery for 61 patients (52%).

Based on how the authors reported the initial patient presentation in the case report or case series, we determined that a total of 96 patients (81%) had severe clinical presentations or complications during pregnancy, 15 patients (13%) had moderate clinical presentations or complications, and four patients (3%) had mild clinical presentations or complications. We determined there was insufficient information to categorize the severity of the presentations or complications in three patients (2.5%). We were unable to identify an environmental or pharmacological exposure that may have been associated with a patient's presentation in 105 patients (89%). Based on the description of patients' clinical outcomes in the included articles, we determined that maternal outcomes were positive in 99 patients (84%), negative in eight patients (7%), and unclear in 11 patients (9%). These categories were defined a priori according to the Methods section and can be viewed in Table 2.

In assessing the publication reasons for the articles we studied, we determined that, of the 107 included articles, 65 (61%) were published as educational material and 26 (24%) as discovery articles; we were unable to determine a clear publication reason for 16 (15%) articles. We present a further breakdown of each classification in Table 3. Of the included

Case reports and case series can be an important part of the scientific discovery journey by communicating novel clinical observations in a structured and comprehensive manner. Our findings suggest that less than one-quarter of these studies in preeclampsia included a clinical discovery component. This begs the question of how today's novel clinical observations are being communicated with the larger scientific and clinical communities. Moreover, the tendency in reporting severe presentations and complications, coupled with positive maternal outcome, suggests that these case reports and case series are unlikely to be a representative sample of the population.

An important finding is the overall low adherence of the included case reports and case series to established reporting guidelines. Most pronounced was the lack of sufficient reporting on patients' characteristics, important measurements of the clinical condition (eg, laboratory results), type of interventions, and post-intervention status. The lack of such information drastically reduces the educational and clinical discovery value of these articles. Ideally, authors should provide sufficient information on all aspects of the clinical encounter with the patients so as to allow clinicians and researchers to understand and potentially replicate or capture the population, intervention, and outcome in future studies. Authors should note any missing information relevant to the disease of which the case report is describing (eg, blood pressure measurement in preeclampsia). Peer-review journals should ideally ensure that case reports and case series are as comprehensively reported as any other form of clinical study design, reporting on patients' characteristics so as to allow a full understanding of risk factors, potential environmental or pharmaceutical exposures, and all the results of relevant tests or examinations. We have outlined these deficiencies and provided recommendations to address them in Table 4.

Table 4 Identified Deficiencies in the Quality of Reporting of Case Reports and Case Series, and Corresponding Recommended Potential Solutions

Case reports and case series have known methodological limitations, whereby they are unable to provide any type of valid statistical inference on the population for which the cases are being described. These limitations have been amplified by misinterpreting the communicated clinical observations as a form of confirmatory evidence rather than exploratory findings that require further investigation.[161] This has led to the gradual loss of favour of case reports and case series, to the extent that certain journals no longer accept case reports for consideration.[162] As our findings suggest, case reports and case series are mostly used as a medium for educational purposes, with little regard to providing the same methodological rigour in comprehensive reporting that is expected from other study designs. This is further devaluing the clinical and scientific value of these important study designs.

As evident by the COVID-19 pandemic, there is an inherent need in the clinical and scientific communities to communicate unusual clinical observations or potentially beneficial forms of clinical management in a new disease area. While some communication of novel clinical observations in relation to COVID-19 have been conducted through the case reports and case series study design approaches, much has occurred in an unstructured manner through various internet-based communication platforms. This may suggest that there is room to rethink the traditional approach of identifying and communicating clinical discoveries.

Strength and Limitations

Through this systematic review, we comprehensively searched and screened all of the identified literature. In addition, we followed a content analysis approach where we developed a codebook to ensure standardization, consistency, and reliability of our data synthesis and assessment.

Limitations in this study include the restriction of the literature search to a five-year period, from 2015 to 2020. This limits the generalizability of our observation to the reviewed period. However, it is arguable that the assessment of the knowledge provided by case series and case reports over a five-year period is sufficient to demonstrate the overall value these methods of scientific communication have in the field of obstetrics. Another limitation is the restriction of our search strategy to the English language. This limits the generalizability of our findings to English-centred obstetrics clinical research. We also included three case reports that were communicated with the publishing journal in a "letter to the editor" format. This represents a minor protocol deviation, where we have excluded study types other than case reports and case series. We included these three case reports, as they were clearly describing clinical encounters with patients in an acceptable case report format.[129,140,142] Finally, only a fraction of the included case reports was considered of high quality (7.7%) and none of the case series were of high quality. This reduced our ability to abstract all relevant data and to construct a meaningful picture of all the included articles, which resulted in some studies being classified as "other" or "unclear" in several categories.

Conclusion

In conclusion, our study suggests that the majority of case reports and case series related to hypertensive disorders of pregnancy do not offer new knowledge and are of poor quality. Only one-quarter of published case reports and case series published from 2015 through 2020 centred on a novel clinical observation or discovery and most of these focused on the management of preeclampsia. Lack of comprehensive reporting and an overall medium to low quality of the included studies limited the utility of these reports as viable sources of information for understanding and managing hypertensive disorders of pregnancy.

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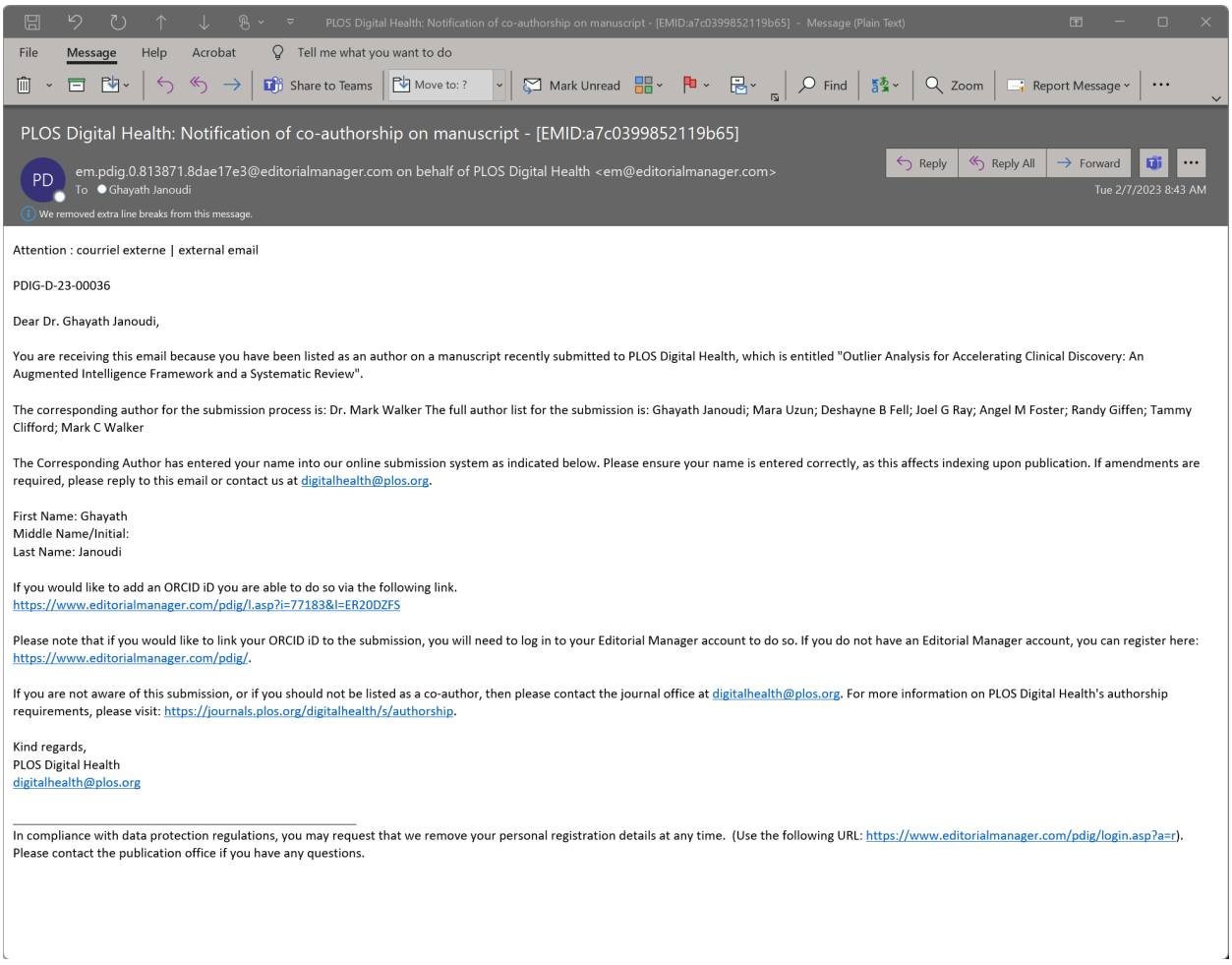
7.3 Appendix 3: Proof of Submission of Second Component Article (Manuscript)



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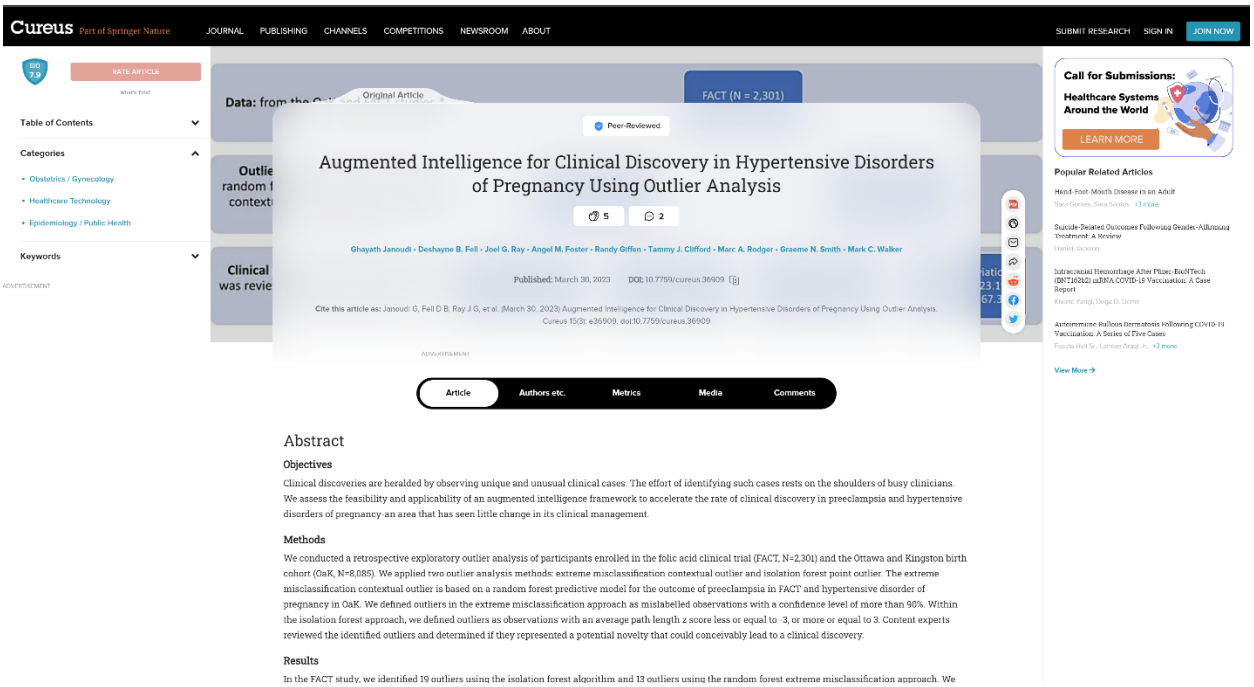
7.4 Appendix 4: Published Version of Third Component Article



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Augmented Intelligence for Clinical Discovery in Hypertensive Disorders of Pregnancy Using Outlier Analysis

Ghayath Janoudi · Deshayne B. Fell · Joel G. Ray · Angel M. Foster · Randy Giffen · Tammy J. Clifford · Marc A. Rodger · Graeme N. Smith · Mark C. Walker

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Abstract

Objectives

Clinical discoveries are heralded by observing unique and unusual clinical cases. The effort of identifying such cases rests on the shoulders of busy clinicians. We assess the feasibility and applicability of an augmented intelligence framework to accelerate the rate of clinical discovery in preeclampsia and hypertensive disorders of pregnancy-an area that has seen little change in its clinical management.

Methods

We conducted a retrospective exploratory outlier analysis of participants enrolled in the folic acid clinical trial (FACT, N=2,301) and the Ottawa and Kingston birth cohort (OaK, N=8,085). We applied two outlier analysis methods: extreme misclassification contextual outlier and isolation forest point outlier. The extreme misclassification contextual outlier is based on a random forest predictive model for the outcome of preeclampsia in FACT and hypertensive disorder of pregnancy in OaK. We defined outliers in the extreme misclassification approach as mislabelled observations with a confidence level of more than 90%. Within the isolation forest approach, we defined outliers as observations with an average path length z score less or equal to -3, or more or equal to 3. Content experts reviewed the identified outliers and determined if they represented a potential novelty that could conceivably lead to a clinical discovery.

Results

In the FACT study, we identified 19 outliers using the isolation forest algorithm and 13 outliers using the random forest extreme misclassification approach. We

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Materials & Methods

We conducted a retrospective exploratory outlier analysis of patients enrolled in the folic acid clinical trial (FACT) and the Ottawa and Kingston (OaK) cohort studies. The folic acid clinical trial was designed to capture preeclampsia diagnosis and progression and thus had a well-structured and focused dataset specific to preeclampsia. The OaK, as a prospective cohort study, represents the real world that aimed to capture myriad pregnancy complications, which may more accurately represent data gathered in usual clinical settings [8,33].

We used two methods within each dataset to identify outliers: isolation forest (a traditional point outliers approach) and extreme misclassification through a random forest predictive model (a contextual outlier approach).

As we are utilizing a predictive model development approach in our contextual outliers method (using the random forest outlier analysis approach), we followed the *transparent reporting of a multivariable prediction model for individual prognosis or diagnosis* (TRIPOD) statement for reporting i.e., transparent reporting of a multivariable prediction model for individual prognosis or diagnosis [34].

Data sources and description of participants

The FACT was a multi-national, double-blind, randomized, placebo-controlled trial completed in Argentina, Australia, Canada, Jamaica, and the UK. It aimed to assess the effects of a 4 mg daily folic acid supplementation on the development of preeclampsia in a high-risk obstetrics population. Between April 2011 and November 2015, a total of 2,464 participants were randomized in a 1:1 ratio to either folic acid or placebo. A total of 2,301 participants were included in the intent-to-treat analysis, with 14.1% of all participants developing new-onset preeclampsia [8].

The OaK was a prospective cohort study conducted from October 2002 to April 2009 that enrolled Canadian pregnant individuals at 12 to 20 weeks gestation who had a viable singleton or twin pregnancy. Data were systematically captured about maternal and infant demographics, maternal health, obstetrical history, and major pregnancy outcomes. One of these outcomes was an adjudicated outcome of hypertensive disorders of pregnancy. A total of 598 participants (7.4%) experienced a hypertensive disorder during pregnancy [33].

Study outcomes in FACT and OaK

The primary outcome of FACT, and that we used herein for the development of a predictive model, was the presence or absence of preeclampsia. Preeclampsia was defined as one of the following: 1) a diastolic blood pressure of ≥ 90 mm Hg on two occasions, four hours or more apart, and proteinuria (more than ++ on dipstick, 24-hour urinary protein ≥ 300 mg, or random protein:creatinine ratio ≥ 30 mg protein/mmol), each arising at 20+ weeks' gestation; 2) development of the hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome; or 3) superimposed preeclampsia namely, a history of pre-existing hypertension before 20 weeks gestation, with new-onset proteinuria at 20+ weeks [8,35].

The OaK cohort evaluated the adjudicated outcome of hypertensive disorders of pregnancy, which included chronic hypertension during pregnancy, pregnancy-induced hypertension, preeclampsia, and HELLP syndrome. The outcome was also used herein [33].

Features engineering

All FACT and OaK variables were used in our study with the exception of those meeting any of the following criteria: 1) a variation or a sub-categorization of the outcome; 2) a variable with over 50% missing data; 3) a variable used to re-categorize an existing continuous variable (e.g., age group when age was present); 4) a variable with only one unique value to all participants (e.g., death when no deaths occurred); 5) a variable where one unique value is present for 99% or more of all observations.

Considering our aim of identifying potential clinical discoveries through outlier analysis, we did not perform further data cleaning.

Results

In the FACT study, we identified 19 outliers using the isolation forest algorithm and 13 outliers using the random forest extreme misclassification approach. We determined that three (15.8%) and 10 (76.9%) were potential novelties, respectively. Out of 8,085 participants in the OaK study, we identified 172 outliers using the isolation forest algorithm and 98 outliers using the random forest extreme misclassification approach; four (2.3%) and 32 (32.7%), respectively, were potential novelties. Overall, the outlier analysis part of the augmented intelligence framework identified a total of 302 outliers. These were subsequently reviewed by content experts, representing the human part of the augmented intelligence framework. The clinical review determined that 49 of the 302 outliers represented potential novelties.

Conclusions

Augmented intelligence using extreme misclassification outlier analysis is a feasible and applicable approach for accelerating the rate of clinical discoveries. The use of an extreme misclassification contextual outlier analysis approach has resulted in a higher proportion of potential novelties than using the more traditional point outlier isolation forest approach. This finding was consistent in both the clinical trial and real-world cohort study data. Using augmented intelligence through outlier analysis has the potential to speed up the process of identifying potential clinical discoveries. This approach can be replicated across clinical disciplines and could exist within electronic medical records systems to automatically identify outliers within clinical notes to clinical experts.

Introduction

Hypertensive disorders of pregnancy, including preeclampsia, are a leading cause of maternal and perinatal morbidity and mortality globally [1]. Despite considerable advancements in elucidating its pathophysiology, the management of preeclampsia has changed minimally over the past two decades [2-7]. Clinical trials of preeclampsia prevention have largely not shown positive results, except for aspirin in the prevention of early-onset preeclampsia [8-10].

Yet clinical observations play a pivotal role in the advancement of medical knowledge [11-13]. The description of an individual clinical case is sometimes the catalyzing step in generating new clinical research, by describing its aberrant or peculiar nature, and the formulation of a hypothesis of why this is so [12-18]. The latter was evident during the COVID-19 pandemic i.e., in understanding the natural history of COVID-19, its detection, and its clinical management [19-23].

Case reports and case series are the conventional study design used by clinicians and researchers to communicate a novel clinical discovery [16-18]. However, their recording and documentation depend on the busy clinician's power of observation [24,25], and the prioritization by the journal editors who tend to offer case reports and case series low priority on the evidence-based medicine hierarchy of publication. Hence, case reports are now mostly used as educational tools [26-28].

Instead of relying on conventional and anecdotal case reports or case series, augmented intelligence uses a machine-based analytic approach to identify potentially new clinical discoveries and flag these to a human content-matter expert. The analytical part of augmented intelligence comprises any statistical or machine-learning method, including outlier analysis. Outlier analysis is currently used for financial fraud detection, network connection anomalies, malware detection, and manufacturing quality control [29,30]. It encompasses various statistical and machine-learning approaches that aim to identify observations that deviate significantly from the majority of other observations [29,30]. In health sciences research, outliers were conventionally handled as statistical noise and were excluded from analyses [31]. However, some outliers may arise from an unrealized and important mechanism or "signal" that holds valuable information and is, thus, worthy of further exploration [29,32].

Our study evaluated contextual outlier analysis using extreme misclassification to discover potentially new phenomena about preeclampsia and hypertensive disorders of pregnancy, using data from a completed randomized clinical trial and a separate cohort study. Extreme misclassification identifies observations that a predictive model mislabels with high confidence as outliers. In addition, the performance of the extreme misclassification contextual outlier analysis was contrasted with a more traditional point outliers detection algorithm to assess which can more aptly identify an outlier potentially useful for clinical discovery.

testing set (with 800 observations), and a validation set (with 301 observations). Similarly, we split the OaK data into training, testing, and validation sets with 3,600, 2,400, and 2085 observations, respectively. We chose the parameters of the model through a random grid search approach, followed by a targeted grid approach that was informed by the results of the random grid search.

We considered those observations that the random forest model misclassified with a confidence level over 0.90 (90%) as outliers. The random forest confidence level represents the proportion of the base learners (or individual trees) that voted for the class. A threshold of 0.90 is an appropriately high threshold to allow for the capture of potentially novel observations whereby the possibility of an unmeasured but influential underlying mechanism could have been the cause of such misclassification.

We then constructed case narrative reports for the identified outliers by returning to the original datasets. Two content-expert researchers (GJ and MW) examined these case narratives and determined if an outlier had the potential of being a novel observation. We assessed each case narrative through several clinical considerations, as well as the clinical likelihood of experiencing the outcome given the available information. Specifically, the two reviewers asked three basic questions when reviewing each observation: 1) Is the presentation of the pregnant individual and the pregnancy journey likely to have led to the observed outcome?, 2) Are there any recorded potential effect modifiers that may have influenced the likely course of pregnancy and the resulting pregnancy outcome?, and 3) Is there any indication of potentially strong effect modifiers that are not recorded, such as an unrecorded medication or an undocumented chronic disease?

For a better understanding of the assessment process, see Table *1*, where we present fictitious examples of case narrative assessments (actual case narratives are not publicly available to safeguard participants' privacy and data).

ID	Assessment	Reasoning	Risk Factors	Interesting Variables
123-456	Potential novelty	The participant had PE, BP measured at 187/103 mm HG, elevated LFT, and required delivery at 34 weeks gestation. The number and type of risk factors do not necessarily justify this presentation. Also, the participant suffers from depression and indicated concomitant medication. Could the concomitant medication predispose the participant to the observed outcome? This would be worth further examination.	Overweight (BMI 29), new partner	SSRIs in concomitant medication, no perinatal vitamins
123-678	Natural deviation	The participant exhibited PE with BP at 140/90 mm HG and 3+ urine dipstick. The participant delivered at 39 weeks gestation with no complications. Considering existing risk factors and positive overall maternal and fetal outcomes, this clinical scenario is not unexpected.	Previous history of PE, obesity (BMI 33), advanced maternal age	Aspirin, folic acid, calcium supplements

Table 1: Fictitious example of clinical assessment of outliers
BP: Blood pressure; LFT: Liver function test; PE: Pulmonary embolism; SSRIs: Selective serotonin reuptake inhibitors

Based on the clinical review (completed by GJ and MW), we classified each observation as either a "potential novelty" or a "natural deviation." We also attempted to explain why either type of observation was captured as an outlier in its given model. Based on this assessment, we reported the proportion of potential novelties detected by each algorithm within each dataset.

Results

Characteristics of participants in FACT and OaK

Participants in both studies were of similar age and shared similar prior pregnancy characteristics such as gravidity and multiple pregnancies. Participants in the FACT study had more risk factors for preeclampsia than those enrolled in OaK, including a higher mean weight (91.6 versus 70.4 kg), a higher proportion of

Considering our aim of identifying potential clinical discoveries through outlier analysis, we did not perform further data cleaning.

Sample size

As the sample sizes for FACT and OaK were fixed, no formal sample size calculation was completed for the current analyses. All 2,301 intent-to-treat participants in the FACT trial were included in our analyses, as well as all 8,085 participants from the OaK cohort [8,33].

Missing data

The overarching imputation strategy for missing data was that they were missing at random. We utilized an iterative imputation approach whereby missing data were imputed via a regression model by treating variables with missing data as a function of other variables. Iterative imputation performs this function in an iterated round-robin fashion in which a variable is designated as the dependent variable and the rest of the variables are designated as independent variables. This is done for every variable with missing data and repeated for a total of 10 iterations. The final imputation is the result of the tenth round [36-38].

We applied an exception to the previous imputation approach when it was clear that the missing data were due to a non-random mechanism. This includes missing data due to non-applicable questions i.e., those questions not posed to certain participants following a previous exclusionary question. This group of missing data cannot be assumed to be missing at random. In these cases, we introduced a numeric value to represent the lack of applicability for a continuous variable (for example, a zero in the case of a number of cigarettes), or a new category in the case of a categorical variable.

Outlier analysis methods

We analyzed each dataset for outliers using two approaches: the isolation forest, and extreme misclassification based on a random forest predictive model.

Isolation Forest

Isolation forest is an ensemble outlier detection recursive algorithm that works by assuming that the number of outliers is small and that they are easily isolated from the rest of the sample. This is conducted through a recursive process, whereby a variable is picked and portioned at random until all observations have been isolated individually. This process produces a decision tree structure in which the path length from the first split until the isolation of the observation can be measured. This process takes place across all variables until all observations have been isolated in all variables, at which point an average path across all variables is calculated for each observation [39]. We determined extreme outliers as observations with an average path length (also known as anomaly score) z score $\leq$ -3, or $\geq$ 3, using the programming language Python 3.9 (Python Software Foundation, Wilmington, DE, USA), together with NumPy, Pandas, and the Scikit-Learn software packages [40-43]. We tuned the isolation forest n_estimators and max_samples parameters by choosing the first value at which the mean and standard deviation of the anomaly score showed the least variations beyond that value, starting from a value of 100 n_estimator and 256 max_samples. For the contamination parameter, which provides the model with an assumption of the extent of outliers to be expected in the sample, it was assumed that no more than 5% of the sample could potentially be an outlier i.e., the contamination value was set at 0.05. Finally, we chose a random state value of 2022 namely, the year in which this analysis was conducted [40,43-45].

Random Forest

This second outlier approach required the development of a predictive model using the random forest algorithm and then leveraging the misclassified observations that the model wrongly predicted with a high level of confidence as an indicator of an outlier status (denoting extreme misclassification). The random forest algorithm is a widely used ensemble learning model in which several base estimators develop decision trees based on a random set of observations and a random set of variables, classifying the observation to the outcome of interest. The collective classification of all the base estimators forms the observation's final prediction [46]. To train, test, and validate the random forest model, the FACT dataset was split into a training set (with 1,200 observations), a testing set (with 800 observations), and a validation set (with 301 observations). Similarly, we split the OaK data into training, testing, and validation sets with

The model generated an anomaly score for each observation, which we used as the basis to determine outliers.

As the isolation forest is an unsupervised model, outcome-based model performance measures could not be calculated.

Random Forest

The FACT dataset included 2,301 participants, 325 (14.1%) of who experienced the outcome of preeclampsia. The OaK dataset included 8,085 participants; 597 (7.4%) experienced the outcome of hypertensive disorders during pregnancy. Tuning the FACT model resulted in the following parameters: bootstrap = False, max_depth = 10, max_features = 40, min_samples_leaf = 2, min_samples_split = 2, and n_estimators = 600. Tuning the model for OaK resulted in the following parameters: n_estimators = 100, min_samples_split = 6, min_samples_leaf = 1, max_features = 10, max_depth = 90, and bootstrap = False.

Using the validation dataset, the FACT random forest model showed a precision of 0.97 and a recall of 0.83 for the outcome of preeclampsia. The OaK random forest model showed a precision of 0.75 and a recall of 0.08 for the outcome of hypertensive disorders of pregnancy. The performance of the models over the entirety of the FACT and OaK datasets is displayed in Table 3.

Class	FACT Precision	FACT Recall	OaK Precision	OaK Recall
No outcome* present	0.99	0.99	0.96	1.00
Outcome* present	0.95	0.93	0.97	0.50

Table 3: Classification report metrics for random forest model applied on the full dataset (training, test, and validation sets)
FACT: Folic acid clinical trial; OaK: Ottawa and Kingston birth cohort

* The FACT outcome was preeclampsia or hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. The OaK outcome was a hypertensive disorder of pregnancy.

Description of outliers

Isolation Forest

Based on setting outliers at a z score of $\leq$ -3 or $\geq$ 3, 19 outliers (0.8%) were identified in the FACT dataset and 172 outliers (2. 1%) were identified in the OaK dataset.

Outliers in each of the datasets display different sets of participants' baseline and demographic characteristics that set them apart from their original datasets. These characteristics are outlined in Table 4.

Variable	FACT Isolation Forest Outliers (N = 19)	FACT Random Forest Outliers (N = 13)	Original FACT Dataset (N = 2,301)	OaK Isolation Forest Outliers (N = 172)	OaK Random Forest Outliers (N = 98)	Original OaK Dataset (N = 8,085)
Age in years, mean (SD)	**30.1 (5.2)**	**29.8 (4.6)**	**31.4 (5.3)**	**25.7 (10.2)**	**30.4 (5.7)**	**30.3 (5.3)**
Weight in kg, mean (SD)	96.9 (28.6)	82.3 (22.8)	91.6 (24.8)	60.1 (30.2)	69.4 (22.8)	68.7 (19.9)
Height in cm, mean (SD)	NA	NA	NA	139.2 (59.3)	163.6 (17.3)	163.7 (14.4)
BMI in kg/m^2, mean (SD)	35.6 (9.4)	31.0 (8.6)	34.0 (11.2)	NA	NA	NA

the FACT study had more risk factors for preeclampsia than those enrolled in OaK, including a higher mean weight (91.6 versus 70.4 kg), a higher proportion of multiple pregnancies (18.6% versus 1.4%), past hypertension (18.4% versus. 1.3%), and a history of preeclampsia (25.3 versus 2.9%), respectively (Table 2).

Variable	FACT (N=2,301)	OaK (N=8,085)
Age in years, mean (SD)	31.4 (5.3)	30.3 (5.3)
Weight in kg, mean (SD)	91.6 (24.8)	68.7 (19.9)
Height in cm, mean (SD)	NA	163.7 (14.4)
Body mass index in kg/m^2, mean (SD)	34.0 (11.2)	NA
G (gravidity), median (interquartile range)	2 (2 to 4)	2 (1 to 3)
T (number of term births), median (interquartile range)	1 (0 to 1)	1 (0 to 1)
P (number of preterm births), median (interquartile range)	0 (0 to 0)	0 (0 to 0)
A (number of abortions/miscarriage), median (interquartile range)	0 (0 to 1)	0 (0 to 2)
L (number of living children), median (interquartile range)	1 (0 to 1)	1 (0 to 1)
M (number of multiple pregnancies), median (interquartile range)	0 (0 to 0)	0 (0 to 0)
Current multiple pregnancy, n (%)	428 (18.6)	361 (4.5)
Assisted reproductive technology pregnancy, n (%)	213 (9.3)	359 (4.4)
History of chronic hypertension, n (%)	428 (18.6)	101 (1.3)
History of gestational diabetes, n (%)	NA	141 (1.7)
History of diabetes mellitus, n(%)	311 (13.5)	NA

Table 2: Maternal and medical characteristics of the FACT and OaK participants
FACT: Folic acid clinical trial; NA: Not applicable; OaK: Ottawa and Kingston birth cohort; SD: Standard deviation

There were no missing data for the outcomes assessed in the random forest model in either dataset. The FACT study contributed a total of 84 variables in both the random forest and isolation forest models; of these, 34 variables had missing values. The OaK cohort contributed a total of 72 variables to the random forest and isolation forest models; of these, 48 variables had missing values. Missing data were handled according to the missing data imputation plan described previously.

Model development, specification, and performance

Isolation Forest

Tuning the isolation forest model produced the following parameters for FACT (N=2,301) data: n_estimator = 300, max_samples = 700. And it produced the following parameters for OaK (N=8,085) data: n_estimator = 900 and max_samples = 256. As per our methods, we used the value of 2,022 as our random_state and 0.05 for contamination. The remaining tuning parameters were left at default values (bootstrap = False, max_features = 1.0, n_jobs = None, warm_start = False). The model generated an anomaly score for each observation, which we used as the basis to determine outliers.

Isolation Forest

Based on setting outliers at a z score of ≤ -3 or ≥ 3, 19 outliers (0.8%) were identified in the FACT dataset and 172 outliers (2. 1%) were identified in the OaK dataset.

Outliers in each of the datasets display different sets of participants' baseline and demographic characteristics that set them apart from their original datasets. These characteristics are outlined in Table 4.

Variable	FACT Isolation Forest Outliers (N = 19)	FACT Random Forest Outliers (N = 13)	Original FACT Dataset (N = 2,301)	OaK Isolation Forest Outliers (N = 172)	OaK Random Forest Outliers (N = 98)	Original OaK Dataset (N = 8,085)
Age in years, mean (SD)	**30.1 (5.2)**	**29.8 (4.6)**	**31.4 (5.3)**	**25.7 (10.2)**	**30.4 (5.7)**	**30.3 (5.3)**
Weight in kg, mean (SD)	96.9 (28.6)	82.3 (22.8)	91.6 (24.8)	60.1 (30.2)	69.4 (22.8)	68.7 (19.9)
Height in cm, mean (SD)	NA	NA	NA	139.2 (59.3)	163.6 (17.3)	163.7 (14.4)
BMI in kg/m^2, mean (SD)	35.6 (9.4)	31.0 (8.6)	34.0 (11.2)	NA	NA	NA
G (gravidity), median (interquartile range)	3 (2 to 4.5)	2 (2 to 3)	2 (2 to 4)	2.8 (2 to 4)	2 (1 to 3)	2 (1 to 3)
T (number of term births), median (interquartile range)	1 (0.5 to 1.5)	1 (0 to 1)	1 (0 to 1)	2 (1 to 2)	0 (0 to 1)	1 (0 to 1)
P (number of preterm births), median (interquartile range)	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)	2 (0 to 2)	0 (0 to 0)	0 (0 to 0)
A (number of abortions/ miscarriage), median (interquartile range)	1 (0 to 1)	0 (0 to 1)	0 (0 to 1)	2 (1 to 2)	0 (0 to 1)	0 (0 to 2)
L (number of living children), median (interquartile range)	2 (1 to 2)	0 (0 to 1)	1 (0 to 1)	2 (1 to 2)	0 (0 to 1)	1 (0 to 1)
M (number of multiple pregnancies), median (interquartile range)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	2 (0 – 2)	0 (0 – 0)	0 (0 – 0)
Current multiple pregnancy, n (%)	7 (36.8)	Suppressed*	428 (18.6)	141 (82.0)	Suppressed*	361 (4.5)

Table 4: Characteristics of isolation forest and random forest outliers and their original datasets
FACT: Folic acid clinical trial; NA: Not applicable; OaK: Ottawa and Kingston birth cohort; SD: Standard deviation

* Cells with medical information pertaining to less than seven aggregate participants are suppressed to protect privacy, and safeguard participants' data.

We noticed that FACT outliers, compared to the original full dataset, had similar mean age, mean weight, and mean BMI; there was a similarity in the proportion of individuals reporting alcohol use during pregnancy, and the proportion of individuals reporting the use of concomitant medications was also similar. Beyond that, outliers had a higher number of previous pregnancies, more twin pregnancies, and a higher proportion of participants with a history of chronic hypertension, diabetes, eclampsia, and smoking. The FACT outliers were less likely to be on folic acid supplementation or aspirin and had their delivery at a lower weeks gestation age than the full dataset. The FACT outliers also had lower mean systolic and diastolic measures than the original dataset, but that also came with a larger standard deviation than observed in the original dataset. All of these observations indicate that FACT outliers appear to be at a higher risk of

lower weeks gestation age than the full dataset. The FACT outliers also had lower mean systolic and diastolic measures than the original dataset, but that also came with a larger standard deviation than observed in the original dataset. All of these observations indicate that FACT outliers appear to be at a higher risk of developing preeclampsia, which is reinforced by higher proportions of FACT outliers experiencing preeclampsia than in the original dataset.

The OaK outliers had similar proportions of individuals with a history of chronic hypertension, gestational diabetes, and history of preeclampsia. Also, they were similarly likely to have been on folic acid supplementation or other concomitant medication. They were less likely to develop preeclampsia or hypertensive disorders during pregnancy. The OaK outliers displayed a markedly lower gestational age at delivery than the original dataset.

We also observed that the outliers identified through the isolation forest had a high proportion of lost-to-follow-up cases. Specifically, there were 12 outliers in the FACT outliers that were lost to follow-up (63.2%) compared to an overall 11.3% in the original full dataset. Similarly, there were 85 outliers in the OaK outliers that were lost to follow-up (49.4%) compared to 2.3% overall lost-to-follow-up in the original full dataset.

Random Forest

Under the random forest model, 13 outliers (0.6%) were identified in the FACT dataset and 98 outliers (1.2%) in the OaK dataset. We have presented the characteristics of these outliers in contrast to the original datasets in Table *4*.

In both datasets, the outliers (identified through the random forest extreme misclassification approach) were of similar age; gravidity, term, pre-term, abortion, living (GTPAL); history of chronic hypertension; folic acid supplementation (outside of FACT intervention); and gestational age at delivery as in their original datasets.

The FACT outliers also had a similar proportion of individuals with a history of diabetes, current aspirin intake, and mean diastolic blood pressure as in the full FACT dataset. The FACT outliers had lower weight and BMI, fewer individuals with multiple pregnancies, fewer pregnancies with assisted reproductive technology, and fewer individuals with a history of smoking. They also had a higher proportion of individuals with a history of preeclampsia, smoking during pregnancy, the use of alcohol during pregnancy, the use of calcium channel blockers, and the use of other medications. Moreover, FACT outliers had higher mean diastolic blood pressure than the original full dataset. The OaK outliers had similar weight, height, history of gestational diabetes, history of preeclampsia, and proportion of participants taking medications.

Under the extreme misclassification approach, FACT and OaK outliers display a much higher proportion of participants with preeclampsia and hypertensive disorders of pregnancy than their full datasets. We also observed that while lost-to-follow-up cases were higher in FACT outliers at two cases (15.4%) than the original dataset (11.3%), this was considerably lower than the proportion of lost-to-follow-up cases in FACT outliers identified through the isolation forest. There were no lost-to-follow-up cases in the OaK outliers.

Assessment of outliers

Upon review of each outlier observation identified in the FACT dataset, we determined that three outliers (15.8%) in the isolation forest and 10 (76.9%) in the random forest extreme misclassification approaches were potential novelties worthy of further investigation. Similarly, upon review of each outlier observation identified in the OaK dataset, we determined that four outliers (2.3%) in the isolation forest and 32 (32.7%) in the random forest extreme misclassification approaches were potential novelties worthy of further investigation. A summary of our assessment can be found in Table *5*. Our findings are further outlined as a flowchart in Figure *1*.

Model	FACT	OaK
Isolation forest		
Total outliers identified, n	19	172

random forest extreme misclassification approaches were potential novelties worthy of further investigation. Similarly, upon review of each outlier observation identified in the OaK dataset, we determined that four outliers (2.3%) in the isolation forest and 32 (32.7%) in the random forest extreme misclassification approaches were potential novelties worthy of further investigation. A summary of our assessment can be found in Table 5. Our findings are further outlined as a flowchart in Figure 1.

Model	FACT	OaK
Isolation forest		
Total outliers identified, n	19	172
Outliers determined as potential novelty, n (%)	3 (15.8)	4 (2.3)
Outliers determined as natural deviation, n (%)	16 (84.2)	168 (97.7)
Random forest extreme misclassification		
Total outliers identified, n	13	98
Outliers determined as potential novelty, n (%)	10 (76.9)	32 (32.7)
Outliers determined as natural deviation, n (%)	3 (23.1)	66 (67.3)

Table 5: Detected outliers and results of the assessment of their case narratives
FACT: Folic acid clinical trial; OaK: Ottawa and Kingston birth cohort

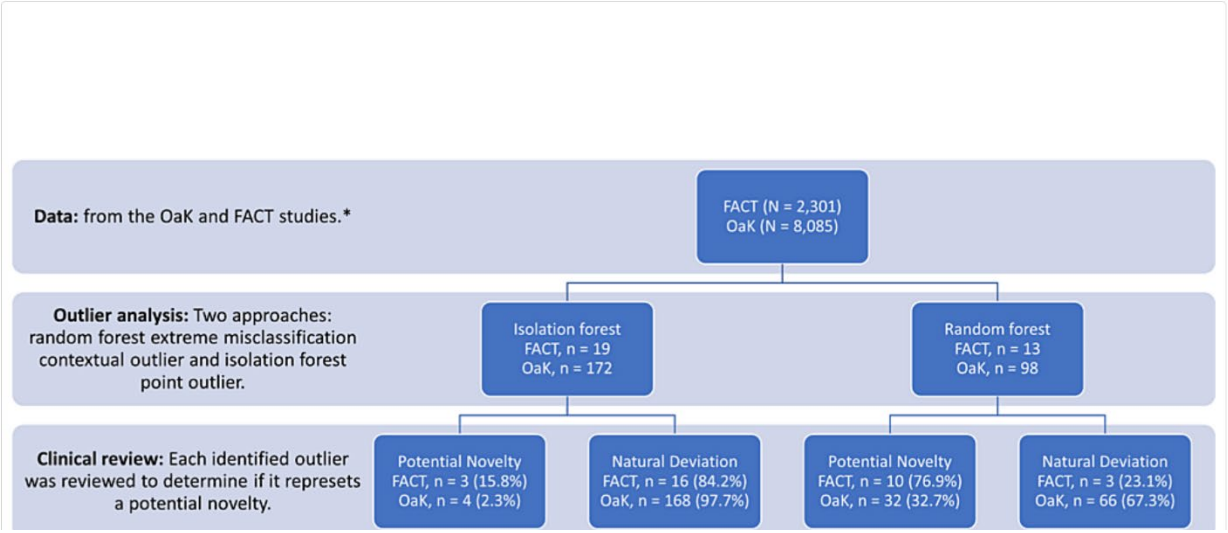

Figure 1: Flowchart of results per analysis stage
* Data from each study were analyzed separately and were not combined

Discussion

In this study, we demonstrated the feasibility of applying an augmented intelligence outlier analysis framework on clinical trials and real-world data. This approach could accelerate the rate of clinical discovery that has traditionally depended on the observation and research skills of individual clinicians. Although the use of outlier analysis for uncovering new clinical insights was first proposed in a publication in 2000 by Laurikkala et al. [47], to the best of our efforts we were unable to find published studies approaching this problem from a contextual outlier analysis perspective using extreme misclassification of a random forest model.

Out of 2,301 participants in the FACT study, we identified 19 outliers using the isolation forest algorithm and 13 outliers using the random forest extreme misclassification approach. Of these, a clinical review determined that three (15.8%) and 10 (76.9%) were potential novelties in the isolation forest and random forest extreme misclassification approaches, respectively, warranting further investigation through source documents review and participant follow-up. Out of 8,085 participants in the OaK study, we identified 172 outliers using the isolation forest algorithm and 98 outliers using the random forest extreme misclassification approach; four (2.3%) and 32 (32.7%), respectively, were potential novelties worthy of further investigation.

In both FACT and OaK datasets, there were more potential novelties within the outliers identified through the random forest extreme misclassification approach (FACT 76.9%, OaK 32.7%) than through the isolation forest approach (FACT 15.8%, OaK 2.3%). Several observations can be made from these results. First, our contextual outlier analysis approach using extreme misclassification has captured a higher number and proportion of potential novelties compared to a standard outlier approach using isolation forest in both datasets. This indicates the advantage of the contextual outlier approach using extreme misclassification. Despite capturing a lesser total number of outliers, it still managed to produce a higher number of potential novelties. This can also be explained by the tendency of the isolation forest algorithm to identify observations that are the easiest to isolate, which manifested in capturing cases that were lost-to-follow-up, withdrew from the study, or experienced early termination. These cases had little information to allow the clinical review to determine if there were any potential novelties.

A second observation was that regardless of the model, we noticed an overall higher proportion of potential novelties in FACT outliers than in OaK outliers. This may be due to the structure and type of variables (features) of the underlying data. For example, the FACT study collected several blood pressure measurements as well as laboratory tests throughout the trial. In contrast, no similar longitudinal variables were collected in the OaK study. This observation is likely to inform future expectations of the proportion of outliers and novelties within datasets based on the dataset design and structure. It is important to note that only one observation within the OaK dataset was identified by both outlier methods; the remaining were unique to each approach. Similarly, all outlier observations within the FACT dataset were unique to each approach with no overlap. This could be explained by the inherently different assumptions and definitions of outliers in each model, whereby the isolation forest depends on unique values in the features. In contrast, the extreme misclassification approach depends on the poor fit of an observation to an outcome classification model.

Based on the results obtained in this study, we believe that the extreme misclassification approach is likely to perform better on both real-world data and clinical trial data. However, considering our previous observation of the minimum overlap in outliers between the two approaches, it is possible that there is room for both approaches to work in parallel to maximize the number of identified potential novelties.

Across all of the datasets and approaches, our clinical review identified 49 observations as potential novelties based on the case narratives of these observations. Ideally, the next step would be to investigate source documentation and potentially follow up with these participants to understand better if an unrecorded factor may have contributed to the unusual clinical observations. Based on the unstructured notes that were added throughout the clinical review of each outlier, there

an observation to an outcome classification model.

Based on the results obtained in this study, we believe that the extreme misclassification approach is likely to perform better on both real-world data and clinical trial data. However, considering our previous observation of the minimum overlap in outliers between the two approaches, it is possible that there is room for both approaches to work in parallel to maximize the number of identified potential novelties.

Across all of the datasets and approaches, our clinical review identified 49 observations as potential novelties based on the case narratives of these observations. Ideally, the next step would be to investigate source documentation and potentially follow up with these participants to understand better if an unrecorded factor may have contributed to the unusual clinical observations. Based on the unstructured notes that were added throughout the clinical review of each outlier, there seems to be a common theme supporting further investigation of the potential role of recorded and unrecorded concomitant medications in contributing to the nature of the observations. Moreover, another theme emerged that indicated that there is room to reassess the traditional importance of certain risk factors when they are simultaneously present with concomitant medication. Both themes can serve as the basis for investigating novelties and formulating scientific hypotheses.

There were several limitations in our study. These include the lack of blinding of the clinical reviewers to the type of model that identified the outlier being assessed. This could have biased the determination of potential novelties in favor of the new approach of extreme misclassification. Blinding the clinical reviewers was not feasible as they needed the model information insight to better understand why a given observation is identified as an outlier. Another important limitation was the lack of a final assessment of the performance of these outlier models in identifying true novel cases that could lead to a clinical discovery. This final assessment can only occur after the determined potential novelties are investigated further through source document review and participants' follow-up, which we were unable to do in this study. Another potential limitation was that the actual outcome for the classification model in both datasets was relatively low (14.1% in FACT and 7.4% in OaK), which may have caused an imbalanced classification, leading to poor recall of the random forest model in both datasets. Within the extreme misclassification approach, the poor recall meant that there was a higher proportion of outliers that were misclassified as not having the outcome compared to outliers that were misclassified as having the outcome. It is also important to note that the classification model is not meant to act as a clinical prediction model and included variables such as the fetal Apgar score, gestational age at delivery, blood pressure measurements, and laboratory results that would not be useful for the development of a clinical prediction model. Finally, it is important to note that the generalizability of the finding is that extreme misclassification performs better than isolation forest and may be limited considering the use of two studies, both of which are in the field of obstetrics.

Conclusions

Unique and unusual clinical observations have been the catalyst for clinical discovery. An efficient way is needed to identify and pursue such observations. In this study, we demonstrated the feasibility, applicability, and potential benefits of utilizing augmented intelligence outlier analysis methods to accelerate the rate of clinical discovery, particularly in preeclampsia and hypertensive disorders of pregnancy. Furthermore, we applied our proposed extreme misclassification contextual outlier analysis approach to real-world and clinical trial data by using the datasets from the FACT and OaK studies as test cases. Our results have shown a higher proportion of potential novelties under the extreme misclassification approach compared to the isolation forest approach in both the clinical trial and real-world data. Our findings suggest that an extreme misclassification contextual outlier approach may have advantages over the classical point outlier analysis approach in identifying cases with potential novelty and thus accelerating the rate of clinical discovery. The application of augmented intelligence using outlier analysis to accelerate the rate of clinical discovery can be implemented in various clinical disciplines and utilized within electronic medical records to identify outliers to clinical experts automatically.

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