EFFECTIVENESS OF CONGENITAL ANOMALY SCREENING BASED ON BASIC RISK FACTORS USING SUPERVISED MACHINE LEARNING

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DEDICATION

This thesis is dedicated to my beloved parents,
my dear husband Muhammad Naveed Aman
and my kids
Muhammad Yousuf Naveed,
Musfirah Naveed,
and Ahmad Yahya Naveed.

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ABSTRACT

In most of the developed countries the national prenatal screening policies for congenital abnormalities has resulted in the reduction of the prevalence rates. However, in most developing countries there is no national prenatal screening policy for congenital abnormalities. This study explores the effect of prenatal screening on the prevalence rates of live birth, fetal death, and termination of pregnancy (TOPFA) on Trisomies and Neural tube defects in Europe. Meanwhile, the prevalence and existing methods for prenatal screening in Malaysia are reviewed. The data used is from the European Surveillance of Congenital Anomalies (EUROCAT) and the Malaysian neonatal registries. The analysis of prevalence rates showed that a prenatal screening policy can reduce the Live Birth (LB) and Fetal Death (FD) prevalence for Trisomies by 77% and 80% respectively, while, for Neural Tube Defects (NTD) by 36% and 38.5%, respectively. The prevalence of Trisomy 21 (T-21) and Neural Tube Defects has increased by 72% and 32% respectively over a period of four years in Malaysia. For this, a risk prediction model using only basic risk factors is developed. This thesis used different supervised machine learning techniques, i.e., logistic regression, random forests, and artificial neural networks (ANN) for the model. Moreover, we also used k-means clustering on our training data and used it to create a Euclidean distance based (supervised) prediction model. The best model according to the results is logistic regression, which can predict T-21 with a sensitivity of 79.75%, specificity of 41.16% and a Balanced Classification Rate (BCR) of 60.46. It is observed that the specificity is low at 41.16% but sensitivity is high which means detection rate is high. The best model for NTD is also logistic regression, which can predict neural tube defect (NTD) with a sensitivity of 68.35%, specificity of 45.32% and a BCR of 59.84%. The risk prediction model of congenital anomalies has a sensitivity of 80%, specificity of 45% and BCR of 63%. The risk prediction model will help the doctors point out the high-risk woman. The accuracy of the prediction model may be improved by adding more predictors, which do not require expensive tests.

ABSTRAK

Di kebanyakan negara maju, dasar pemeriksaan pranatal nasional untuk keabnormalan kongenital telah mengakibatkan pengurangan kadar prevalensi. Malangnya di kebanyakan negara membangun tidak ada dasar pemeriksaan pranatal nasional untuk keabnormalan kongenital. Kajian ini menerangkan kesan pemeriksaan pranatal terhadap kadar prevalensi kelahiran hidup, kematian janin, dan penamatan kehamilan (TOPFA) mengenai kecacatan dan kecacatan tiub Neural di Eropah. Sementara itu, kelaziman dan kaedah sedia ada untuk pemeriksaan pranatal di Malaysia dikaji semula. Data yang digunakan adalah dari Pengawasan Eropah bagi Anomali Kongenital (EUROCAT) dan pendaftaran neonatal Malaysia. Analisis kadar prevalensi menunjukkan bahawa pemeriksaan pranatal dapat mengurangkan kelaziman Live Birth (LB) dan kematian janin (FD) untuk Trisomies masing-masing sebanyak 77% dan 80% manakala untuk Kecacatan Tube Neural (NTD) sebanyak 36% dan 38.5 %, masing-masing. Penyebaran Trisomy 21 (T-21) dan Kecacatan Tabung Neural telah meningkat masing-masing sebanyak 72% dan 32% dalam tempoh empat tahun di Malaysia. Untuk ini, model ramalan risiko yang menggunakan hanya faktor risiko asas dibangunkan. Tesis ini menggunakan teknik pembelajaran mesin yang diawasi yang berbeza, iaitu, regresi logistik, hutan rawak, dan rangkaian saraf buatan (ANN) untuk model terlebut. Selain itu, kami juga menggunakan k-means clustering pada data latihan kami dan menggunakannya untuk membuat model prediksi jarak jauh (diselia) Euclidean. Model terbaik berdasarkan hasilnya adalah regresi logistik, yang dapat meramalkan T-21 dengan kepekaan 79.75%, kekhususan 41.16% dan Kadar Klasifikasi Seimbang (BCR) sebanyak 60.46. Adalah diperhatikan bahawa kekhususan adalah rendah pada 41.16% tetapi kepekaan tinggi yang bermakna kadar pengesanan adalah tinggi. Model terbaik untuk NTD adalah juga regresi logistik, yang dapat meramalkan kecacatan tabung neural (NTD) dengan kepekaan 68.35%, kekhususan 45.32% dan BCR 59.84%. Model ramalan risiko anomali kongenital mempunyai kepekaan sebanyak 80%, kekhususan 45% dan BCR sebanyak 63%. Model ramalan risiko akan membantu para doktor menunjuk wanita berisiko tinggi. Ketepatan model ramalan boleh diperbaiki dengan menambah lebih banyak ramalan, yang tidak memerlukan ujian mahal.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

β-HCG	-	Beta Human Chorionic Gonadotropins
ACOG	-	American Congress of Obstetricians and Gynecologists
AFP	-	Alpha Fetoprotein
ANN	-	Artificial Neural Network
BCR	-	Balanced Classification Rate
CVS	-	Chorionic Villus Sampling
EUROCAT	-	European Surveillance of Congenital Anomalies
FD	-	Fetal Death
LB	-	Live Birth
MNR	-	Malaysian Neonatal Registry
MOH	-	Ministry of Health
NT	-	Nuchal Translucency
NTD	-	Neural Tube Defect
PAPP-A	-	Pregnancy Associated plasma Protein
PHC	-	Primary Health Care
SB	-	Still Birth
T-13	-	Trisomy 13
T-18	-	Trisomy 18
T-21	-	Trisomy 21
TOPFA	-	Termination of Pregnancy for Fetal Anomaly
UE	-	Unconjugated Estradiol

LIST OF SYMBOLS

B	Number of sample trees
F	Classification tree
c_i	Collection of centroid
S_i	Data point for centroid

CHAPTER 1

INTRODUCTION

1.1 Overview

Congenital anomalies are the diagnosed defects, in an infant or newborn which are usually manifested as physical, mental disability or majorly deaths [1]. Some of the birth defects are life threatening and babies rarely survive the neonatal period. Nowadays, with advances in medical field the prenatal diagnosis of congenital anomalies has become more accessible and reliable using noninvasive or invasive methods [2]. This chapter includes a discussion of the effect of prenatal screening and diagnosis of congenital anomalies on its prevalence rate in developed countries and the benefits and factors for not having a national screening policy in a developing country like Malaysia. Moreover, it includes a review on different models used around the globe for prediction of congenital anomalies in pregnant women and why can't those models be used in developing countries. Conclusively, the main problem statement that drives this research has been stated with the support of pieces of evidence from the recent research.

1.2 Study Background

Congenital anomalies contribute a significant proportion of infant mortality and morbidity as well as fetal mortality. One of the fundamental aspects of antenatal care is prenatal screening and diagnosis in order to detect congenital anomalies early in gestation. Every year approximately 8 million children are born with congenital anomalies [2]. An estimated 3.3 million of them die and approximately 3.2 million

suffer from deformities later in life [2]. Whereas, in developing countries the congenital anomaly is not considered as a public health issue though the number of deaths and disabilities due to anomalies is no less than infections with 5% of total neonatal deaths in 2015 were due to congenital anomalies [3].

In most of the developed countries, prenatal screening for abnormalities is an essential test of antenatal care [4]. These prenatal screening tests are offered to all women even if they don't have any risk factor [5]. Moreover these tests are offered free of charge [5], which could be one of the reason why these tests are accepted by people in developed countries.

Congenital defects can lead to long-term disabilities, chronic illnesses and economic burden on parents. Factors such as genetic infections, environmental factors, nutritional deficiencies, maternal age and socioeconomic status are among the causes of congenital disorders [3] or it could be multifactorial. Thus medical professionals are required to use a combination of fetal monitoring and screening methods to plan the best possible treatment and follow up care for the mother and baby. It is one of the major causes for deaths under 5 years of age and there was an increase of 15% deaths from year 1994 to 2006 in children under 5 years of age [6, 7]. This may be a big trauma for parents to have a child with abnormalities after 9 months of pregnancy

In developing countries like Malaysia there is no national prenatal screening and diagnostic policy for congenital abnormalities. Prenatal screening tests are available in a few laboratories and private clinics/hospitals but they are highly expensive for people to afford and are not covered by insurance.

In Malaysia pregnant women are seen by primary health care doctors and routine antenatal care includes identification of risk factors along with basic health and blood screening and no prenatal screening for congenital anomalies[8]. Ultrasound is also a part of routine antenatal screening method with inconsistent timing, for example in some centers the 20th week anomaly scan is not done [9, 10].

Although most of the congenital anomalies are incurable, monitoring, screening, and early detection of anomalies (such as the Trisomy 21, Trisomy 18, Trisomy 13, and neural tube defects etc.) could provide several benefits. These benefits include reassurance of a normal pregnancy, making an informed decision, counseling of parents, adequate time for the parents to prepare and plan for proper health care services [4], chance to terminate the pregnancy, better planning and preparation by the doctors, and avoiding unnecessary caesarian section. Prenatal screening for genetic anomalies is also recommended to high-risk pregnant women.

The method and protocol for prenatal screening and diagnosis varies from country to country. Many developed countries such as the United States of America [11] and major countries in Europe have adopted prenatal screening to detect congenital problems in the early stages of pregnancy resulting in a decrease in the infant and neonatal mortality due to anomalies and increase in the prenatal diagnosis of these anomalies [12].

Malaysia is a well-organized country with free medical services for its citizens. Government sectors as well as private setups have good obstetric and neonatal care facilities. However, prenatal screening tests are not offered in Malaysia due to factors such as legal, social, religious and ethical considerations, lack of expertise and proper equipment, and management options [8]. Public hospitals are considered good but pregnant women in Malaysia are seen by primary health care doctors who have basic medical knowledge and are not specialized doctors [8]. There is a high chance that they might miss the signs of anomalies on scans. No prenatal screening tests are available in public hospitals, although a few private hospitals offer these tests. Therefore they have to send samples to outside laboratories, which are highly expensive and cannot be afforded by lower and middle class people. There is no prenatal screening policy in the country [8] even though congenital anomalies is one of the major cause for deaths under 5 years of age contributing 27.2 % according to the department of statistics Malaysia [13] and birth defects are one of the main cause for perinatal and neonatal deaths and it accounts for 17.5% of these deaths [14].

Furthermore, there are numerous research studies and data in the developed countries on the prevalence, risk factors, screening, diagnostic and treatment options of congenital anomalies while developing countries are still lacking with proper data collection including Malaysia [15] and no data has been recorded or updated on congenital anomalies after the year 2008 in Malaysia [16].

Prenatal screening tests such as amniocentesis and chorionic villus sampling are not offered in Malaysia due to factors such as legal, social, religious and ethical considerations, lack of expertise and proper equipment, and management options [8]. Therefore, non-invasive prenatal screening tests such as first and second trimester biochemical markers, nuchal Translucency is measured through ultrasound (done between 10^{th} to 14^{th} week of gestation) and anomaly scan done at 20^{th} week of gestation would be the best choice. Yet, there are three major issues with using these tests in developing countries: firstly, these non-invasive tests have a high cost and the affordability is a concern. Secondly, these tests are not widely available in developing countries. Finally, the lack of appropriate training, adherence to a standard technique, and ongoing assessment of image quality [17] may result in missing accurate ultrasound measurements. Therefore, most developing countries rely on indicators such as maternal age, gestational age, ethnicity etc. for initial risk assessment.

Hence, this study came up with the solution of a prediction model using basic risk factors for the detection of high-risk women for having babies with congenital anomalies. This study used the famous supervised machine learning techniques, logistic regression, random forest, K-means clustering, artificial neural networks for developing the prediction model. In chapter 2 a brief description of the techniques that are used for the risk prediction model for trisomy 21 and neural tube defects has been given.

1.3 Problem Statement

In spite of the fact that congenital anomalies are one of the leading causes of infant mortality, there is no national prenatal screening policy in developing countries. Prenatal screening and diagnosis for congenital anomalies is not widely available in Malaysia, screening and diagnostic tests offered for detection of congenital anomalies are expensive [18] and cannot be afforded without government subsidy. Pregnant women usually present late for their first antenatal checkup due to which the golden period, i.e., between 10^{th} to 14^{th} week of gestation for checking Nuchal Translucency through ultrasound is missed [18]. Prenatal screening is also not widely accepted in Malaysia due to cost, legal issues and ethical, cultural and religious beliefs [8, 18-20]. Only private hospitals and some laboratories offer prenatal screening tests but they are highly expensive and lower and middle class people cannot afford them. In developed countries, the introduction of prenatal screening policy has reduced the infant and under 5 mortality rate. However, in developing countries there are a few issues due to which implementation of a national policy for prenatal screening policies might be a problem. Firstly, the lack of expertise, secondly the lack of widely available tests in the country, third and by far the most important is affordability. Hence, a prediction risk model for the risk assessment of pregnant women for congenital anomalies using only basic risk factors is needed in developing countries keeping in view all these problems. The prediction model used in developed countries use biochemical markers along with radiological scans, which cannot be used in developing countries because of cost and other issues. Thus, this study will focus on using basic risk factors for detection rate of risk in pregnant women for congenital anomalies using various risk prediction models. This study used different techniques of supervised machine learning to come up with the best model to be used for risk assessment of congenital anomalies in developing countries. The model will be totally free of cost as the variables can be easily obtained through history from the pregnant woman during her antenatal visits. It will help highlight the high-risk pregnancies without adding any cost so that timely management can be done. The various techniques of supervised machine learning used in this study are given in the Table 1.1.

Table 1.1 Supervised machine learning techniques

Supervised Machine Learning Techniques
1. Logistic Regression 2. Random Forest 3. K means clustering 4. Artificial Neural Network

1.4 Research Objectives

The objectives of this study are as follows:

i. To compare effectiveness of total prenatal screening implementations in Europe and in Malaysia on prevalence of congenital anomalies.
ii. To determine the risk of congenital anomalies by basic risk factors in pregnant women using supervised machine learning risk prediction models.

1.5 Scope of the Study

The focus of this research is to study the effect of total prenatal screening implementation on the prevalence rates of these congenital anomalies in Europe and also in Malaysia. Moreover, this study will focus on using basic risk factors for detection of risk of Trisomy 21 and neural tube defects in pregnant women in developing countries by using prediction models developed by supervised machine learning. The various techniques (logistic regression, K means clustering, Artificial Neural Network and random forest) used for the prediction model will help with developing the best one to be proposed for using in developing countries.

1.6 Significance of the Study

Congenital anomalies are one of the major causes responsible for infant and neonatal mortality and morbidity. This study showed that developed countries with national screening policies had significantly low rates of anomalies though the rates of termination of pregnancy for fetal anomalies (TOPFA) was high in those countries. These policies helped decrease the rate of live birth prevalence and also there was reduction in the infant mortality rates in the developed countries. In developing countries such as Malaysia, there are no national screening policies for prenatal screening and diagnosis of congenital anomalies. The purpose of this research was to design a risk prediction model keeping in mind all the factors due to which there is no national screening policy in developing countries. This prediction model only used basic risk factors to calculate the risk for having trisomy 21 and neural tube defects as well any congenital anomaly. The previous models use risk factors along with biochemical markers to calculate the risk in pregnant women for having anomalies. However, it is not possible to screen every woman in developing countries due to many factors, in which cost is the most important factor. This prediction model is highly beneficial for screening pregnant woman without any extra cost. This will not only help the health professional point out the high-risk woman, but also help pregnant woman to be screened and marked as low or high-risk patient. Moreover the pregnant women can be sent to a facility where better planning, counseling of the parents and timely management of the baby with anomalies can be done.

REFERENCES

[1] World Health Organization. (2016). *Congenital Anomalies*. Available: http://www.who.int/mediacentre/factsheets/fs370/en/

[2] R. Carmona, (2005). "The global challenges of birth defects and disabilities," *The Lancet,* 366 (9492), . 1142-44.

[3] World Health Organization, (2015). "Methods and data sources for child causes of death," Available: http://www.who.int/healthinfo/global_burden_disease/ChildCOD_method_2000_2015.pdf.

[4] J. Yu, (2012). "A systematic review of issues around antenatal screening and prenatal diagnostic testing for genetic disorders: women of Asian origin in western countries," *Health & Social Care in the Community,* 20(4), 329-346.

[5] "Special Report: Prenatal Screening Policies in Europe," EUROCAT2010, Available: http://www.eurocat-network.eu/content/Special-Report-Prenatal-Screening-Policies.pdf.

[6] Ministry of Health. (1993-2003). *Under 5 Deaths in Malaysia*. Available: http://www.crc.gov.my/wp-content/uploads/documents/report/StudyOnUnder5DeathsinMsia_1993-2003.pdf

[7] L. Anthony, N. Lee, S. Ambu, and L. Hakim, (2013). "A trend analysis of major congenital anomalies in Penang, Malaysia," *International e-Journal of Science, Medicine & Education, Malaysia,* 7(2), 33-40.

[8] Ministry of Health. (2017). *Maternal Screening For Foetal Abnormality, Malaysia*. Available: www.moh.gov.my/update2017/739.pdf

[9] Ministry of Health, (2013). "Perinatal care,Malaysia," Available: http://fh.moh.gov.my/v3/index.php/component/jdownloads/send/18-sektor-kesihatan-ibu/224-perinatal-care-manual-3rd-edition-2013?option=com_jdownloads.

[10] Ministry of Health, (2017). "Use of Ultrasound in antenatal care,Malaysia," Available: http://www.moh.gov.my/update2017/720.pdf.

[11] G. Latendresse and A. Deneris, (2015). "An Update on Current Prenatal Testing Options: First Trimester and Noninvasive Prenatal Testing," *Journal of Midwifery & Women's Health,* 60(1), 24-36.

[12] EUROCAT. (2010). *Prenatal Screening Policies in Europe*. Available: http://www.eurocat-network.eu/content/Special-Report-Prenatal-Screening-Policies.pdf

[13] Department of Statistics. *Malaysia*. Available: www.dosm.gov.my

[14] J. J. Ho, M. K. Thong, and N. K. Nurani, (2006). "Prenatal detection of birth defects in a Malaysian population: Estimation of the influence of termination of pregnancy on birth prevalence in a developing country," *Australian and New Zealand Journal of Obstetrics and Gynaecology,* 46(1), 55-57.

[15] M. Noraihan, M. See, R. Raja, T. Baskaran, and E. Symonds, (2005). "Audit of birth defects in 34,109 deliveries in a tertiary referral center.," *Medical Journal of Malaysia,* 60(4), 460-468.

[16] MNNR. *Report of Malaysian National Neonatal Registry*. Available: http://www.acrm.org.my/mnnr/journals.php

[17] G. Ceska , J. Sonek, K. Nicolaides, and J. P, (2012). "Screening at 11-13+6 weeks' gestation," *Ceska gynekologie / Ceska lekarska spolecnost J. Ev. Purkyne (Ceska Gynekol),* 77(2), 92-104.

[18] A. Sulaiha and I. Nazimah, (2008)."Prenatal Screening for Fetal Anomalies: The Malaysian Perspectives," *Malaysian Journal of Obstetrics & Gynaecology,* 8(16), .1-10.

[19] G. K. Shapiro, "Abortion law in Muslim-majority countries: an overview of the Islamic discourse with policy implications," *Health Policy and Planning,* vol. 29, no. 4, pp. 483-494, 2014.

[20] M. Q. Joy Vink *Obstetric Imaging: Fetal Diagnosis and Care* Second ed. Elsevier.

[21] K. D. Honore and G. Ester, (2014). "Trends in prenatal diagnosis of anomalies among live births over a 30-year period," (in en), *Journal of Reproductive Biology and Health,* 2(1).

[22] B. NY, C. IG, and T. MK, (2013). "Neural Tube Defects in Malaysia: Data from the Malaysian National Neonatal Registry. ," *Journal of Tropical Pediatrics,* 59(5), 338-342.

[23] B. Azman *et al.*, (2007). "Cytogenetic and clinical profile of Down syndrome in Northeast Malaysia," *Singapore Medical Journal,* 48(6), 550-554.

[24] Statistics, (2018). "Mean age of mother at first live birth,Malaysia," Department of statitics, Available: https://www.dosm.gov.my/v1/index.php?r=column/cthemeByCat&cat=165&bul_id=eUM5SGRBZndGUHRCZTc2RldqNGMrUT09&menu_id=L0pheU43NWJwRWVSZklWdzQ4TlhUUT09.

[25] M. E. Weijerman and J. P. De Winter, (2015). "Clinical practice: The care of children with Down syndrome," *European Journal of Pediatrics,* 169(12), 1445-1452.

[26] A. Cereda and J. Carey, (2012). "The trisomy 18 syndrome," *Orphanet Journal of Rare Diseases,* 7(81).

[27] Wikipedia. (2019). *Down Syndrome*. Available: https://en.wikipedia.org/wiki/Down_syndrome

[28] N. Greene and A. Copp, (2014). "Neural tube defects," *Annual Review of Neuroscience,* 37, 221-242.

[29] R. D. Wilson, F. Audibert, J.-A. Brock, C. Campagnolo, J. Carroll, and L. Cartier, (2014). "Prenatal Screening, Diagnosis, and Pregnancy Management of Fetal Neural Tube Defects," *Journal of Obstetrics and Gynaecology Canada,* 36(10), 927-939.

[30] EUROCAT. (2005). *Prenatal Screening Policies in Europe*. Available: http://www.eurocat-network.eu/content/Special-Report-Prenatal-Diagnosis.pdf

[31] European Observatory on Health Systems and Policies. (2006). *Policy Brief Screening in Europe*. Available: http://www.euro.who.int/__data/assets/pdf_file/0007/108961/E88698.pdf

[32] EUROCAT. *European network of population-based registries for the epidemiological surveillance of congenital anomalies*. Available: https://eu-rd-platform.jrc.ec.europa.eu/eurocat

[33] F. A. Dalia, I. Hamizah, N. Zalina, S. L. Yong, and A. Mokhtar, (2016). "A Retrospective Review of 25 cases of Lethal Fetal Anomalies.," *International Medical Journal Malaysia,* 15(1), 19-23.

[34] N. IS, C. MM, and B. NY, (1995). "Cytogenetic study of Malaysian neonates with congenital abnormalities in Maternity Hospital Kuala Lumpur.," *Medical Journal Malaysia,* 50(1), 52-58.

[35] C. F. Ngim, N. M. Lai, I. HIshamshah, and R. Vanassa, (2013). "Attitudes towards prenatal diagnosis and abortion in a multi-ethnic country: a survey among parents of children with thalassaemia major in Malaysia," *Journal of Community Genetics,* 4(2), 215-221.

[36] Wikipedia. (2019). *Logistic regression*. Available: https://en.wikipedia.org/wiki/Logistic_regression

[37] Wikipedia. (2019). *Random Forest*. Available: https://en.wikipedia.org/wiki/Random_forest - Algorithm

[38] A. Trevino. (2016). *Introduction to K-means Clustering*. Available: https://www.datascience.com/blog/k-means-clustering

[39] M. Dziubek. (2018). *Let me introduce you to neural networks*. Available: https://towardsdatascience.com/let-me-introduce-you-to-neural-networks-fedf4253106a

[40] M. A. Ferguson□Smith and J. R. W. Yates, (1984). "Maternal Age Specific Rates for Chromosome Aberrations and Factors," *Prenatal diagnosis,* 4(7), 5-44.

[41] I. Merkatz, H. Nitowsky, J. Macri, and W. Johnson, (1984)."An association between low maternal serum alpha-fetoprotein and fetal chromosomal abnormalities," *American Journal of Obstetrics and Gynaecology,* 148(7), 886-894,

[42] N. Wald, J. Densem, L. George, S. Muttukrishna, and P. Knight, (1996). "Prenatal screening for Down's syndrome using Inhibin-A as a serum marker," *Prenatal Diagnosis,* 16(2), 143-53,.

[43] F. D. Malone *et al.*, (2005). "First-Trimester or Second-Trimester Screening, or Both, for Down's Syndrome," *New England Journal of Medicine,* 353(19), 2001-11.

[44] M. Brizot, R. Snijders, J. Butler, N. Bersinger , and K. Nicolaides, (1995). "Maternal serum hCG and fetal nuchal translucency thickness for the prediction of fetal trisomies in the first trimester of pregnancy," 102(2), 127-132.

[45] S. Cicero, P. Curcio, P. Aris, J. Sonek, and K. Nicolaides, (2001) "Absence of nasal bone in fetuses with trisomy 21 at 11-14 weeks of gestation: an observational study," *The Lancet,* 358(9294), 1665-1667.

[46] A. Matias, C. Gomes, N. Flack, N. Montenegro, and N. K.H, (1998). "Screening for chromosomal abnormalities at 10–14 weeks: the role of ductus venosus blood flow," *Ultrasound in Obstetrics and Gynaecology,* 12(6), 380-384,.

[47] I. C. Huggon, D. B. DeFigueiredo, and L. D. Allan, (2003). "Tricuspid regurgitation in the diagnosis of chromosomal anomalies in the fetus at 11–14 weeks of gestation," *Heart,* 89(9), 1071-1073.

[48] U. Omer, K. Heysem, G. Fikret, and G. V. Fusun, (2013). "Prenatal risk assessment of Trisomy 21 by probabilistic classifiers," Haspolat, Turkey.

[49] Rebecca Jeanne Gersnoviez, (2011). *Optimizing a First-Trimester Predictive Model for Trisomy 21*. Proquest, Umi Dissertation Publishing.

[50] C. Andreas, H. Kypros, and N. Christos, (2016). "First Trimester Noninvasive Prenatal Diagnosis: A Computational Intelligence Approach," 20(5), 1427-1438.

[51] J. Haddow, G. Palomaki, G. Knight, J. Williams, W. Miller, and A. Johnson, (1998). "Screening of maternal serum for fetal Down's syndrome in the first trimester," *The New England Journal of Medicine,* 338(14), 955-61,

[52] Wapner RJ, (2005). "First trimester screening: the BUN study," *Semin Perinatol,* 29(4), 236-9.

[53] N. Wald, C. Rodec, A. Hackshaw, J. Walters, and L. Chitty, (2003). "First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS)," *Health Techonology Assessment,* 7(11), 1-77.

[54] F. Malone, N. Wald, A. Jacob, H. Robert, A. David, and H. Christine, (2003). "First- and second-trimester evaluation of risk (faster) trial: principal results of the NICHD multicenter down syndrome screening study," *American Journal of Obstetrics & Gynecology,* 189(6), S56.

[55] K. Avgidou, A. Papageorghiou, R. Bindra, K. Spencer, and K. Nicolaides, (2005). "Prospective first-trimester screening for trisomy 21 in 30,564 pregnancies," *American Journal of Obstetrics & Gynecology,* 192(6), 1761-7.

[56] H. Tan, S. Wen, X. Chen, K. Demissie, and M. Walker, (2007)."Early prediction of preterm birth for singleton, twin, and triplet pregnancies.," *European Journal of Obstetrics, gynaecology and Reproductive Biology,* 31(2), 132-7.

[57] A. Singh, S. Arya, H. Chellani, K. Aggarwal, and R. Pandey, (2014). "Prediction model for low birth weight and its validation.," *Indian Journal of Pediatrics,* 81(1), 24-8.

[58] H. Li *et al.*, (2017)."An artificial neural network prediction model of congenital heart disease based on risk factors: A hospital-based case-control study.," *Medicine,* 96(6), e6090.

[59] Tin Tin Su, Mohammadreza Amiri, Farizah Mohd Hairi, Nithiah Thangiah, Awang Bulgiba, and H. A. Majid1, (2015). "Prediction of Cardiovascular Disease Risk among Low-Income Urban Dwellers in Metropolitan Kuala Lumpur, Malaysia," *Biomed Research International Journal,*.

[60] H. Yadav and N. Lee, (2013). "Maternal factors in predicting low birth weight babies," *The Medical journal of Malaysia,* 68(1), 44-47.

[61] A. A. o. Pediatrics, (1999). "Folic Acid for the Prevention of Neural Tube Defects," *Pediatrics,* 104(2), 325.

[62] National Perinatal Epidemiology and Statistics Unit, "Neural tube defects in Australia: prevalence before mandatory folic acid fortification," Available: https://npesu.unsw.edu.au/surveillance/neural-tube-defects-australia-prevalence-mandatory-folic-acid-fortification.

[63] I. Zaganjor *et al.*, (2016). "Describing the Prevalence of Neural Tube Defects Worldwide: A Systematic Literature Review," *PLOS ONE,* 11(4),.

[64] Centre for Disease Control and Prevention, "Down Syndrome," Available: https://www.cdc.gov/ncbddd/birthdefects/DownSyndrome.html.

[65] F. Coppedè, (2016). "Risk factors for Down syndrome," *Archives of Toxicology,* 90(12), 2917-2929.

[66] National Down Syndrome Society, "Down's Syndrome," Available: http://www.ndss.org/Down-Syndrome/What-Is-Down-Syndrome/.

[67] C. Irving, A. Basu, S. Richmond, J. Burn, and C. Wren, (2008). "Twenty-year trends in prevalence and survival of Down syndrome," *Eur J Hum Genet,* 16(11), 336-1340.

[68] A. Cereda and J. C. Carey, (2012). "The trisomy 18 syndrome," *Orphanet Journal of Rare Diseases,* 7(1), 81.

[69] G. Imataka, A. Nitta, H. Suzumura, H. Watanabe, H. Yamanouchi, and O. Arisaka, (2007). "Survival of trisomy 18 cases in Japan," *Genet Couns,* 18.

[70] M. Loane *et al.*, (2013). "Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening," *European Journal of Human Genetics,* 21(1), 27-33.

[71] O. A. Houlihan and K. O'Donoghue, (2013). "The natural history of pregnancies with a diagnosis of Trisomy 18 or Trisomy 13; a retrospective case series," *BMC Pregnancy and Childbirth,* 13, 209-209.

[72] "2005 American heart association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: pediatric advanced life support," *Pediatrics,* 117.

[73] D. Carvajal and P. Rowe, (2010). "Sensitivity, specificity, predictive values, and likelihood ratios.," *Pediatrics in Review,* 31(12), 511-3.

[74] A. Tharwat., (2018). "Classification assessment methods," *Applied Computing and Informatics*.

[75] P. A. Boyd, C. DeVigan, B. Khoshnood, M. Loane, E. Garne, and H. Dolk, (2008). "Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome," *Bjog,* 115(6), 689-696.

[76] R. C. Reinsch, (1997). "Choroid plexus cysts-association with trisomy: prospective review of 16,059 patients," *Am J Obstet Gynecol,* 176.

[77] Nuffield Council on Bioethics, (2017). "Non invasive prenatal testing:ethical issues," Available: http://nuffieldbioethics.org/wp-content/uploads/NIPT-ethical-issues-full-report.pdf.

[78] MIchael Kutner, (2004). *Applied Linear Regression Model*. McGraw-Hill Irwin.

[79] A. Albasri, S. Prinjha, R. McManus, and J. Sheppard, (2018). "Hypertension referrals from community pharmacy to general practice: Multivariate logistic regression analysis of 131 419 patients," *British Journal of General Practice,* 68(673), 541-550.

[80] L. Wulsin, P. Horn, J. Perry, J. Massaro, and R. D'Agostino, (2015). "Autonomic imbalance as a predictor of metabolic risks, cardiovascular disease, diabetes, and mortality.," *The Journal of Clinical Endocrinology and Metabolism,* 100(6), 2443-2448.

[81] Z. Algamal and M. Lee, (2015). "Regularized logistic regression with adjusted adaptive elastic net for gene selection in high dimensional cancer classification. ," *Computer in Biology and Medicine,* 67, 136-145.

[82] H. Delacour, A. Servonnet , A. Perrot, J. Vigezzi, and J. Ramirez, (2005). "ROC (receiver operating characteristics) curve: principles and application in biology," *Annales De Biologie Clinique (Paris),* 63(2), 145-154.

LIST OF PUBLICATIONS

1. **M. T. Khattak**, E. Supriyanto,M. N. Aman, R. H. Al-Ashwal, (2019). "Predicting Down Syndrome and Neural Tube Defects Using Basic Risk Factors", Medical and Biological Engineering and Computing, (Impact Factor: 2.039)
2. **M. T. Khattak**, E. Supriyanto, and R. H. Al-Ashwal, (2018). A Logistic Regression Prediction Model of Congenital Anomalies Based on Basic Risk Factors, under review in ARPN Journal of Engineering and Applied Science.