INTELLIGENT SYSTEMS APPROACH FOR CLASSIFICATION AND MANAGEMENT OF PATIENTS WITH HEADACHE

by

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DECLARATION

I, Ahmed Kaky, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm this has been indicated in the thesis.

Ahmed Jasim Mohammed Kaky

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ABSTRACT

Primary headache disorders are the most common complaints worldwide. The socioeconomic and personal impact of headache disorders is enormous, as it is the leading cause of workplace absence. Headache patients' consultations are increasing as the population has increased in size, live longer and many people have multiple conditions, however, access to specialist services across the UK is currently inequitable because the numbers of trained consultant neurologists in the UK are 10 times lower than other European countries. Additionally, more than two third of headache cases presented to primary care were labelled with unspecified headache. Therefore, an alternative pathway to diagnose and manage patients with primary headache could be crucial to reducing the need for specialist assessment and increase capacity within the current service model. Several recent studies have targeted this issue through the development of clinical decision support systems, which can help non-specialist doctors and general practitioners to diagnose patients with primary headache disorders in primary clinics. However, the majority of these studies were following a rule-based system style, in which the rules were summarised and expressed by a computer engineer. This style carries many downsides, and we will discuss them later on in this dissertation.

In this study, we are adopting a completely different approach. The use of machine learning is recruited for the classification of primary headache disorders, for which a dataset of 832 records of patients with primary headaches was considered, originating from three medical centres located in Turkey. Three main types of primary headaches were derived from the data set including Tension Type Headache in both episodic and chronic forms, Migraine with and without Aura, followed by Trigeminal Autonomic Cephalalgia that further subdivided into Cluster headache, paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing. Six popular machine-learning based classifiers, including linear and non-linear ensemble learning, in addition to one regression based procedure, have been evaluated for the classification of primary headaches within a supervised learning setting, achieving highest aggregate performance outcomes of AUC 0.923, sensitivity 0.897, and overall classification accuracy of 0.843.

This study also introduces the proposed HydroApp system, which is an M-health based personalised application for the follow-up of patients with long-term conditions such as chronic headache and hydrocephalus. We managed to develop this system with the supervision of headache specialists at Ashford hospital, London, and neurology experts at Walton Centre and Alder Hey hospital Liverpool. We have successfully investigated the acceptance of using such an M-health based system via an online questionnaire, where 86% of paediatric patients and 60% of adult patients were interested in using HydroApp system to manage their conditions. Features and functions offered by HydroApp system such as recording headache score, recording of general health and well-being as well as alerting the treating team, have been perceived as very or extremely important aspects from patients' point of view.

The study concludes that the advances in intelligent systems and M-health applications represent a promising atmosphere through which to identify alternative solutions, which in turn increases the capacity in the current service model and improves diagnostic capability in the primary headache domain and beyond.

TABLE OF CONTENTS

ACKNOWLEDGEMENT ..... *vi*

ABSTRACT ..... *ivi*

TABLE OF CONTENTS ..... *vi*

LIST OF FIGURES ..... *ix*

LIST OF TABLES ..... *x*

ABBREVIATIONS ..... *xi*

Chapter 1: INTRODUCTION **1**

1.1. Overview 1

1.2. Problem statement 2

1.3. Research question 3

1.4. Research aims and objectives 3

1.5. Research scope 6

1.6. Research contributions 6

1.7. Structure of the thesis 7

Chapter 2: HEADACHE DISORDERS **9**

2.1. Introduction 9

2.2. Types of headaches 9

2.3. Primary headache disorders 12

2.3.1. Migraine 12

2.3.2. Tension-type headache 14

2.3.3. Trigeminal Autonomic Cephalalgias (TACs) 16

3.3.3.1 Cluster headache 16

3.3.3.2 Paroxysmal hemicrania 18

3.3.3.3 SUNCT 18

2.4. Presentation and comparison 19

2.5. Secondary headache disorders 21

2.6. Chapter summary 22

Chapter 3: LITERATURE REVIEW **23**

3.1. Introduction 23

3.2. Intelligent driven modules to diagnose headaches 23

3.2.1. Neurologist expert system (NES) 24
3.2.2. Expert system based headache solution (ESHS) 24
3.2.3. A guideline-based DSS for headache diagnosis 25
3.2.4. Validation of a guideline-based DSS for headache diagnosis 25
3.2.5. Case-based reasoning DSS for headache diagnosis 25
3.2.6. Hybrid intelligent reasoning DSS 26
3.2.7. Automatic DSS for the classification of primary headaches 26
3.2.8. Other headache diagnostic modules 27
3.3. Evaluation and justifications 28
3.4. Chapter summary 31

Chapter 4: DATA PREPARATION 33
4.1. Introduction 33
4.2. Data description 33
4.3. Outliers' detection 37
4.4. Missing Data 42
4.4.1. Missing data mechanism 42
4.4.2. Processing of missing data 47
4.4.3. Multiple imputations 50
4.4.4. Dichotomous and categorical variables 58
4.5. Data normalisation 59
4.6. Chapter summary 60

Chapter 5: PREDICTIVE MODELS 61
5.1. Introduction 61
5.2. Feature selection 61
5.2.1. Information gain (IG) 63
5.2.2. Symmetrical Uncertainty (SU) 65
5.2.3. Multilayer perceptron (MLP) 66
5.2.4. A majority vote 68
5.3. Feature analysis 69
5.3.1. Continuous features 70
5.3.2. Discrete features 71
5.3.2.1 Headache characteristic 72
5.3.2.2 Headache location 73

5.3.2.3 Photophobia and phonophobia 75
5.3.2.4 Nausea and vomiting 76
5.3.2.5 Neurological examination and Fundoscopy test 77
5.3.3. Summary of analysis 80
5.4. Class balancing and Binarization 83
5.5. Performance metrics 85
5.6. Predictive models 87
5.6.1. Tension type headache vs. all 88
5.6.2. Migraine vs. all 90
5.6.3. TACs vs. all 90
5.7. Pooling and discussion 91
5.8. Chapter summary 103

Chapter 6: HEADACHE FOLLOW-UP 104
6.1. Introduction 104
6.2. The HydroApp system 104
6.3. HydroApp system architecture 105
6.3.1. The client application 107
6.3.2. The server application 109
6.3.3. Central database 110
6.3.4. Data privacy and security 112
6.3.5. Authentication and authorisation 113
6.3.6. Application usability 115
6.4. HydroApp system in use for clinical follow-up study 115
6.5. The benefits of HydroApp system 119
6.6. Chapter summary 121

Chapter 7: CONCLUSION AND FUTURE WORK 122
7.1. Conclusion 122
7.2. Future work 124

Appendix A: Separate Variance t Tests 125

Appendix B: HydroApp Dashboard snippets 133

Appendix C: List of publications 137

REFERENCES 139

LIST OF FIGURES

FIGURE 1-1: RESEARCH MAP 5
FIGURE 2-1: TYPES OF HEADACHE 10
FIGURE 3-1: TYPES OF CLINICAL DECISION SUPPORT SYSTEMS 29
FIGURE 4-1: DATA OUTLIERS 39
FIGURE 4-2: DATA WITHOUT OUTLIERS 41
FIGURE 4-3: OVERALL SUMMARY OF MISSING DATA 44
FIGURE 4-4: OUR VISION IN HANDLING MISSING DATA 49
FIGURE 5-1: A TYPICAL MLP NEURAL NETWORK 66
FIGURE 5-2: INTERVAL PLOT OF LEVEL MEANS AND CONFIDENCE INTERVALS OF HEADACHE DURATION AND FREQUENCY 70
FIGURE 5-3: HOW HEADACHE PATIENTS DESCRIBE THEIR PAIN 73
FIGURE 5-4: PARTS OF THE HUMAN SKULL [3] 74
FIGURE 5-5: GROUPING THE LOCATIONS OF PAIN 75
FIGURE 5-6: THE PRESENCE OF PHOTOPHOBIA AND PHONOPHOBIA 76
FIGURE 5-7: THE PRESENCE OF NAUSEA AND VOMITING 77
FIGURE 5-8: NEUROLOGICAL EXAMINATION RESULT 79
FIGURE 5-9: FUNDUSCOPIC TEST RESULT 79
FIGURE 5-10: PERFORMANCE OF MLS (TTH VS. ALL) 89
FIGURE 5-11: ROC PLOTS FOR THE MODELS 93
FIGURE 5-12: POOLED TPR, PPV AND F1 MEASURES 95
FIGURE 5-13: POOLED ACC AND AUC 96
FIGURE 5-14: RPART MODEL OF MIGRAINE VS. ALL 97
FIGURE 5-15: CLASS ERROR RATE OF RF MODEL WITH 100 TREES 99
FIGURE 5-16: FEATURES IMPORTANCE PLOT BY RF MODEL 100
FIGURE 5-17: TRAINING ERROR OF ADA MODEL OVER A 100 ITERATIONS 100
FIGURE 6-1: SIMPLE OVERVIEW OF 3-TIER APPLICATIONS 106
FIGURE 6-2: THE BIG PICTURE 107
FIGURE 6-3: HYDROAPP SCREENSHOTS 1 108
FIGURE 6-4: HYDROAPP SCREENSHOTS 2 108
FIGURE 6-5: EXAMPLE OF PATIENTS PROFILES 109
FIGURE 6-6: DASHBOARD TO PRESENT PATIENTS' DATA 110
FIGURE 6-7: STAR SCHEMA OF APPS' TABLES 112
FIGURE 6-9: AUTHENTICATION PROCESS 114

LIST OF TABLES

TABLE 2-1: THE DIFFERENCE BETWEEN THE PRIMARY AND SECONDARY HEADACHE .. 11
TABLE 2-2: MIGRAINE WITHOUT AURA 13
TABLE 2-3: MIGRAINE WITH TYPICAL AURA 14
TABLE 2-4: TENSION-TYPE HEADACHE 16
TABLE 2-5: CLUSTER HEADACHE 17
TABLE 2-6: COMPARISON OF MIGRAINE, TENSION-TYPE AND TACS 20
TABLE 3-1: SUMMARY OF DIAGNOSTIC MODULES 30
TABLE 4-1: DATA ATTRIBUTES 35
TABLE 4-2: VARIABLE SUMMARY [A,B] 45
TABLE 4-3: EM MEANS[A] 47
TABLE 4-4: IMPUTATION MODELS 53
TABLE 4-5: STATISTICS FOR MI 56
TABLE 4-6: MODEL SUMMARY 58
TABLE 4-7: DESCRIPTIVE STATISTICS OF QUANTITATIVE ATTRIBUTES AFTER NORMALISATION 60
TABLE 5-1: TOP-RANKED FEATURES USING IG 64
TABLE 5-2: TOP-RANKED FEATURES USING SU 65
TABLE 5-3: THE HIGHEST PERFORMING FEATURE SUBSET USING MLP 68
TABLE 5-4: FEATURES EVALUATION (ALL FEATURES ARE CONSIDERED) 69
TABLE 5-5: SELECTED FEATURES EVALUATION 81
TABLE 5-6: CONFUSION MATRIX 86
TABLE 5-7: PERFORMANCE METRICS 87
TABLE 5-8: TTH VS. ALL RESULTS USING HOLDOUT METHOD 89
TABLE 5-9: MIGR VS. ALL RESULTS USING HOLDOUT METHOD 90
TABLE 5-10: TACS VS. ALL RESULTS USING HOLDOUT METHOD 91
TABLE 5-11: POOLED RESULTS 94
TABLE 5-12: THE TRANSLATION OF FIGURE 4-16 INTO A SET OF RULES 98
TABLE 5-13: COMPREHENSIVE COMPARISON OF PREDICTIVE MODELS 103
TABLE 6-1: VERY OR EXTREMELY IMPORTANT ASPECTS OF USING TECHNOLOGY FOR FOLLOW-UP 118

ABBREVIATIONS

GPs	**General Practitioners**
NHS	UK's National Health Service
WHO	World Health Organisation
IHS	International Headache Society
ICHD	International Classification of Headache Disorders
AMPP	American Migraine Prevalence and Prevention
SIGN	Scottish Intercollegiate Guidelines Network
BASH	The British Association for the Study of Headache
NICE	National Institute For Health and Clinical Excellence
BASICS	The British Antibiotic and Silver Impregnated Catheters for VP Shunts
VPS	Ventriculoperitoneal Shunts
Hydro-OQ	Hydrocephalus Outcome Questioner
PRO	Patient Reported Outcome
RCT	Randomised Control Trial
SWAT	Study Within a Trial
HIT-6	Headache Impact Test
MIDAS	Migraine Disability Assessment Test
MIGR	Migraine
CM	Chronic Migraine
EM	Episodic Migraine
MwA	Migraine with Aura
MwoA	Migraine without Aura
TTH	Tension-type Headache
TACs	Trigeminal Autonomic Cephalalgias
CH	Cluster Headache
PH	Paroxysmal Hemicrania
SUNCT	Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing
OSAS	Obstructive Sleep Apnoea syndrome
TrPs	Trigger Points
FHP	Forward Head Posture
M-health	Mobile health
e-health	Electronic health
DSS	Decision Support Systems
ML	Machine Learning
CBR	Case-Based Reasoning
RBFL	Rule-based Fuzzy Logic
RPART	Classification and Regression Tree
ADA	Adaptive Boosting

RF	Random Forest
SVM	Support Vector Machine
LOGR	Logistic Regression
LINR	Liner regression
MLP	Multilayer perceptron
GA	Genetic Algorithm
KNN	K-Nearest Neighbour
IQR	Interquartile Range
MCAR	Missing Completely at Random
MAR	Missing at Random
NMAR	Not Missing at Random
EM	Expectation Maximisation
FCS	Fully Conditional Specification
MI	Multiple Imputations
MEL	Maximum Likelihood Estimation
MCMC	Markov Chain Monte Carlo
LOCF	Last Observation Carried Forward
IG	Information Gain
SU	Symmetrical Uncertainty
ANOVA	Analysis Of Variance
OVA	One Versus All
ROC	Receiver Operating Curve
AUC	Area Under The ROC Curve
PPV	Positive Predictive Value
TPR	True Positive Rate
FPR	False Positive Rate
FNR	False Negative Rate
CP	Complexity Parameter
OOB	Out-Of-Bag error

CHAPTER 1: INTRODUCTION

1.1. Overview

Headache is the commonest neurological symptom presenting to general practitioners (GPs) and neurologists. It can be a symptom of many different diseases and disorders, with a variety of forms, frequency and severity from mild that disappear easily, to severe and repeated disabling headache that can be painful and debilitating in some individuals [1, 2]. Since 1988, The International Headache Society (IHS) has established a standardised terminology and consistent operational diagnostic criteria for a wide range of headaches under the term of International Classification of Headache Disorders [3]. These criteria are derived according to an international consensus of headache experts and have been accepted as a gold standard for headache diagnosis. The current revision of IHS criteria, i.e. ICHD-3 beta was published in 2013.

Headaches, according to IHS criteria, are broadly classified into primary and secondary. Primary headaches, such as migraine (MIGR), tension-type headache (TTH) and trigeminal autonomic cephalalgias (TACs), are the most common in the community and they are not related to any underlying medical condition, where the headache itself is the disorder [3-5]. While secondary headache disorders occur secondarily to another medical condition, some of which may be life threatening and therefore require quick and accurate diagnosis. Secondary headache is extremely rare and represents less than 1% of the population who experience headaches [6, 7].

In the UK, the lifetime prevalence of headaches is 90% of the general population [4], and the annual headache consultation is 4.4% of all primary care consultations [6]. The personal, social and economic burden of headache disorders is enormous. Migraine is classed by the World Health Organisation (WHO) as one of the 20 leading causes of disability amongst adults [8]. There are an estimated 6.7 million people living with migraine in England [9], and around 83,000 people miss work or school every day, because of headache, which is equivalent to 20 million days of lost productivity per year [10], with a cost to the UK economy that may exceed 1.5 billion pound a year [11].

1.2. Problem statement

Patients with headaches usually do not seek medical help from their GPs until the headache really affects their quality of life, and when they do seek medical help, the diagnosis is usually incorrect and the condition improperly managed. This was clearly shown by a UK study of the primary care database, which revealed that 70% of headaches were not assigned a diagnostic label [6]. Another similar study conducted in the USA revealed that 69% of headache sufferers were labelled with unspecified headache in the primary care [12]. The findings of these two studies made clear that GPs encounter difficulty in the diagnosis of headaches, which in turn may increase the pressure on the specialist neurology clinics.

Headache referrals currently account for around a third of outpatient referrals to specialist neurology clinics across the UK [7, 13]. However, access to specialist services across the country is currently inequitable. This is due to the fact that the numbers of trained consultant neurologists in the UK are 10 times lower than other European countries [11], and this problem is exacerbated further by the inequitable distribution of specialist headache clinics between regions in England [14].

Patients with chronic headache are usually asked to fill in headache diaries or outcome measures such as Headache Impact Test (HIT-6) and Migraine Disability Assessment Test (MIDAS) on a regular basis; specialists use these forms to measure the impact of headache on a patient's life. However, within publicly funded health care systems such as the UK's National Health Service (NHS), long term monitoring in neurology clinics or GPs appears not to be possible for all patients with chronic headache due to the continued decline in funding over the past decade. This was shown by a study conducted in 2016, which revealed that more patients in Britain will be unable to obtain an appointment with their GPs due to the decline in GPs funding by 17% of the NHS budget [15].

Accordingly, an alternative pathway to diagnose and manage patients with headache is necessary to improve patient care as well as to conquer the challenges facing the NHS. This is what Hedley Emsley, a consultant neurologist at the Department of Neurology, Royal Preston Hospital, has confirmed in his online article for the Health service journal (HSJ) [13]. Therefore, this study proposes an intelligent solution to overcome these difficulties via two main points. First, the use of Machine Learning

(ML) to improve the diagnosis of primary headaches, in which a set of ML classifiers will be used to build several diagnostic or predictive models from a real-world dataset of patients with primary headaches. The second point is adopting mobile health (M-health) technology to provide an effective platform for long-term patient follow-up. This study aims to contribute to this gap in knowledge.

ML classifiers can learn and gain knowledge from previous experiences and/or through identifying patterns in medical data. They are able to learn the important features of a given dataset, i.e. primary headaches that are diagnosed by specialists, in order to make predictions about other data, i.e. new headache cases, which were not a part of the original training set. The ML based diagnostic model will act as a decision support to assist non-specialist doctors or nurses in GPs' surgeries to make accurate diagnosis with respect to patients with primary headaches. This in turn could reduce the need for specialist assessment and thus referrals to neurology clinics.

Likewise, M-health application represents an intelligent solution, and holds potential to allow specialists to monitor a larger number of patients with chronic headache than would be possible within the current service model. It could replace traditional paper based headache diaries and outcome measures and provide several advantages including improved monitoring of historical responses to therapies, improved recording of side effects and it can be adapted to improve communication between patients and clinicians. A remote follow-up using M-health technology can promote the quality of care given to this category of patients as well as engaging them in their condition management. Therefore, our proposed pathway is a great step toward optimal patient care and proper clinical management.

1.3. Research question

Is it possible to use machine-learning methods supported by M-health technology for diagnosing and follow-up of patients with headache?

1.4. Research aims and objectives

The main aim of this study is to provide a robust and effective diagnostic support model to improve the diagnosis or classification of primary headache disorders using ML methods, and initialising a user-friendly central control platform that would

support and facilitate the headache specialist's task and increase their productivity with respect to long-term follow-up and clinical management of patients with headache. We will work towards these aims by addressing the following objectives and as shown in the research map (Figure 1-1).

1. Review and comprehend primary headache disorders in accordance with the latest clinical guidelines, in addition to initialising an overall comparison among their types.
2. Review and evaluate various research studies and intelligent decision support systems (DSS) that aimed at improving the classification or the diagnosis of primary headache disorders. These studies or systems are going to be assessed and compared against each other in order to identify their points of strength and weakness and examine their intelligent module as well as the overall efficiency and outcomes.
3. Prepare for a data acquisition procedure. This is probably the most challenging part of the study, which requires establishing links or getting in contact with dozens of research groups, specialised headache centres and hospitals as well as headache associations such as the British Association for the Study of Headache.
4. Design the data quality framework to the highest possible standard. This framework outlines and describes almost all of the essential measures for data processing and analysis, making use of the most advanced and sophisticated computational and statistical approaches. This step helps to ensure that the data is clean enough, legitimate and the ML classifiers can use the most relevant features.
5. Develop and evaluate several diagnostic or predictive models using a number of ML classifiers trained with data records of patients with primary headaches. These intelligent predictive models are going to be assessed using different performance matrices as a way to demonstrate their discriminatory power. An overall comparison can bring about the best performing predictive model.
6. Design and develop an M-health based application along with a central control system prototype to enable an effective and affordable means for an ongoing follow-up of patients with chronic headaches. This long-term

monitoring system permits information to flow easily between patients and their care providers. This personalised system enables patients to engage in their condition management.

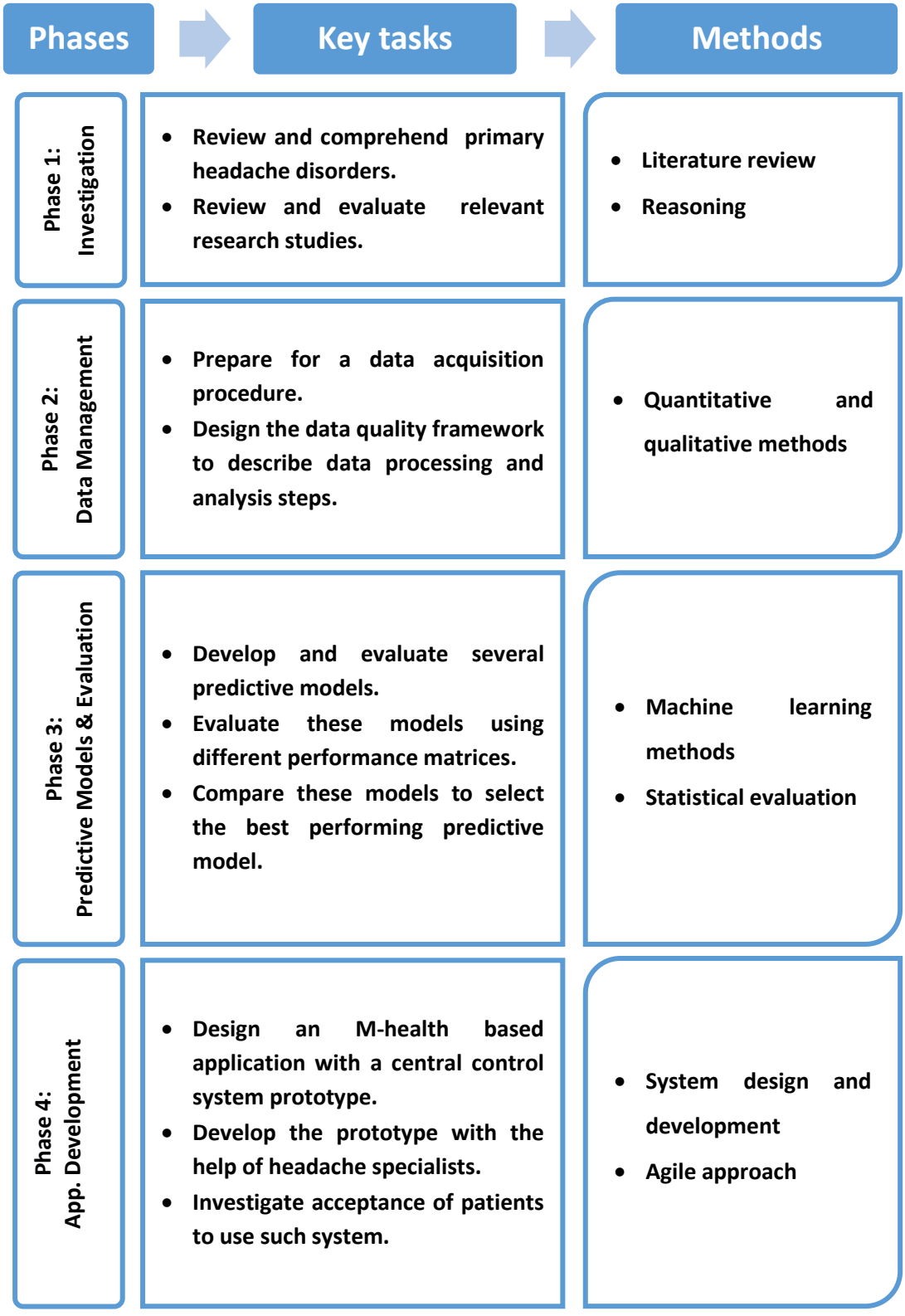


Figure 1-1: Research map

1.5. Research scope

This study focuses on creating an ML-based diagnostic model for classifying the most common primary headache disorders, such as migraine, tension-type headache and trigeminal autonomic cephalalgias, according to the following points:

1. Primary headaches are the main cause of headaches in the community, where the headache itself is the disease [4, 7].
2. Brain imaging is not always necessary in the diagnosis of primary headaches, considering the fact that the disease has no impact that leads to macroscopic change in general terms [16].
3. Primary headache disorders are diagnosed by defining the clinical features of episodes, pain patterns and associated sign and symptoms and then applying them to the established definitions, or clinical rules and guidelines for diagnosis, which are formulated by IHS and accepted worldwide [17].

Moreover, this study also focuses on providing a simple yet powerful method to enable a long-term monitoring and follow-up of patients with chronic headache via adopting the M-health application. We will design and develop this application to help in the follow-up of headaches whether it was a disease or symptom of another disease such as hydrocephalus, i.e. primary and secondary headaches.

1.6. Research contributions

This study holds two novel contributions. The first contribution is to improve the diagnosis of primary headache disorders in the primary care clinics by applying advanced intelligent methods. Developing such an intelligent diagnostic model will have a significant impact on NHS services as it will decrease the need for specialist assessment, and can be used to train non-specialist and junior doctors to improve their decision-making procedure. The development of such novel intelligent diagnostic model will pass through many stages such as a proper configuration of clinical data including data cleansing, preparation and processing. In addition to investigating and evaluating a range of machine learning approaches to examine their capability, validity and accuracy of classification.

The second novel contribution is to establish a personalised platform for long-term monitoring and follow-up of patients with chronic headaches at secondary clinics.

This platform will be developed using M-health technology and from a headache specialist's perspective. The new proposed platform provides an on-the-go analysis of a patient's data, which improves a doctor's productivity and decision making as well.

A clinical team from NHS will be involved in the design and development of this novel follow-up system. This advanced technology will be used to replace the traditional way of follow-up and data collection, as it allow patients to manage their condition and will ensure that patient-reported outcomes are recorded efficiently. It will be assumed that the standard use of such smartphone based PRO (patient reported outcome) will be able to reduce unnecessary visits to neuroscience centres, whilst enabling and improving communication between patient and health care provider and follow by creating appropriate clinical thresholds for alerting medical staff of changes in symptoms or of changes of behaviours and of symptoms automatically.

1.7. Structure of the thesis

This thesis is organised in seven chapters, each chapter addressing a different element of the study.

Chapter 1 introduces the research problem along with the aims and objectives of this study. It also identifies the research scope and describes the structure of this thesis.

Chapter 2 reviews the literature to investigate recent studies that target the diagnosis of primary headache disorders using different intelligent techniques. This chapter compares and evaluates these studies to explore their advantages and drawbacks.

Chapter 3 is introductory to headache disorders. In this chapter, we review and discuss the main types of primary headaches according to the globally agreed criteria of IHS. Chapter 3 ends with an overall comparison of the various types of primary headaches.

Chapter 4 presents the data acquisition procedure and the comprehensive data processing stages. In this chapter, we start by identifying outliers, addressing missing data using multiple imputations and eventually data normalisation approach.

Chapter 5 starts with a feature selection process, in which a majority vote of three different methods is considered to retain the most relevant features. Chapter 5 then analyses these features to define their discriminative power. Before starting training ML classifiers and creating predictive models, chapter 5 also investigates class distribution to improve the generalisation approach in the learning phase. Chapter 5 ends with pooling the results and provides an overall comparison of the predictive models.

Chapter 6 introduces the HydroApp system for self-management of patients with long-term conditions such as chronic headache or hydrocephalus. This chapter discusses the technical aspects of the HydroApp system along with the ability of using such a system for the benefit of the NHS. Finally, chapter 7 concludes this study, where we provide recommendations for future work.

CHAPTER 2: HEADACHE DISORDERS

2.1. Introduction

Headache, or cephalalgia in the medical term, is the sensation of pain in any region of the head. It can affect all age groups in both severe and chronic settings with numerous underlying causes and variety of forms, frequency and severity from mild that disappear easily to severe and repeated disabling headache that can be painful and debilitating in some individuals [1]. Headache can be a symptom of many different diseases and disorders that make the discrimination between potentially life-threatening and non-serious causes complicated, even to the health professionals [18]. It may be a sharp pain, boring ache or throbbing sensation, show up progressively or suddenly, and it may last less than 60 minutes or for many days. This chapter presents an overview of the main types of primary headache disorders along with their clinical features and the operational diagnostic criteria. An overall comparison of primary headache disorders according to the most up-to-date criteria of IHS and scientific studies is also presented in this chapter.

2.2. Types of headaches

Headache is the commonest neurological symptom presenting to GPs and neurologists [1, 18]. According to the Scottish Intercollegiate Guidelines Network (SIGN), lifetime prevalence of headache is 90% of the general UK population [4]. There are several types of headaches; in fact, according to WebMD [19], there are 150 different types of headaches. These types can happen for many reasons, have a distinct or overlapping set of symptoms and require different kinds of treatment. Classifying the type of headache can be challenging, but allows optimal treatment for the patient [20]. A systematic approach to headache classification and diagnosis is therefore the first step to optimal patient care, proper clinical management, effective investigation and more focused research [21, 22].

In 2013, the International Headache Society (IHS) released the beta edition of the third International Classification of Headache Disorders (ICHD) [3]. ICHD includes a standardised terminology and consistent operational diagnostic criteria for a wide range of headache disorders [23]. These criteria were drawn up based on an international consensus of headache experts and have been accepted worldwide as a

gold standard for headache diagnosis. The IHS uses straightforward diagnostic criteria, which are explicit, unambiguous, accurate and with as little scope for interpretation as possible. ICHD-3 beta was published to synchronise with the World Health Organization's next revision of the International Classification of Diseases (ICD-11), which is due by 2018. The last version of international classification of headache disorders (ICHD-2) was incorporated into the previous International Classification of Diseases (ICD-10).

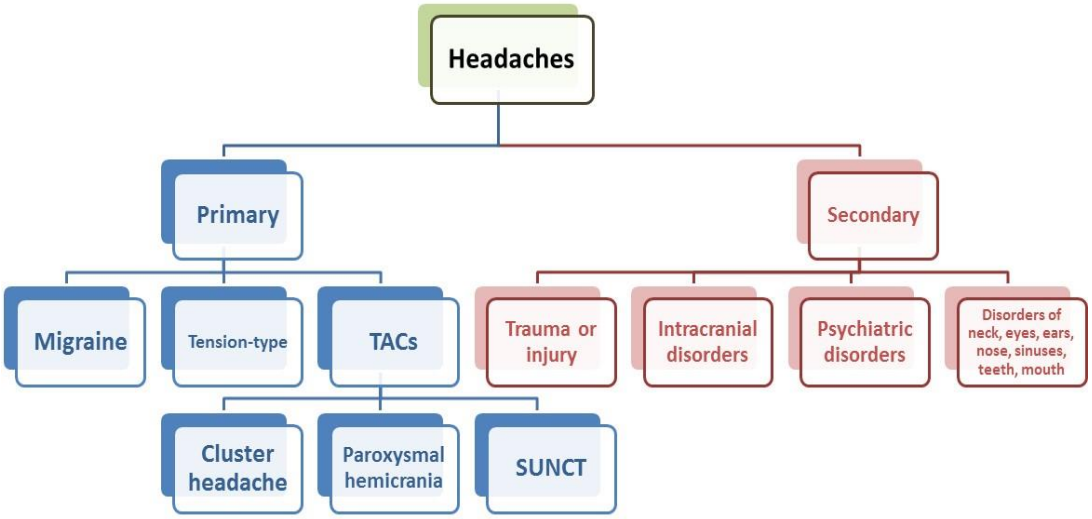


Figure 2-1: Types of headache

The ICHD-3 beta divides headache disorders into primary and secondary headaches, and these two broad categories are further subdivided into particular headache forms. Primary headache disorders include migraine, the trigeminal autonomic cephalalgias (TACs), and tension-type headache. TACs category includes cluster headache (CH), paroxysmal hemicrania (PH) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT).

Headache history can play an important role in the diagnosis of primary headache disorders, since there are no diagnostic tests that can be beneficial [4, 5, 24, 25]. Tracking a headache history requires time to elicit basic information, and not finding the time is probably the cause of the most misdiagnosis. A simple and helpful way to tack headache history is to request keeping of a diary over a couple of weeks when the patient first presents with headache [26]. A good headache history will enable the medical expert to understand a pattern, which consequently leads to the accurate diagnosis. Ravishankar in his work [5] has reviewed the art of history taking in

patients with headache across different settings. He mentioned that the routine history taking starts with a set of regular questions that will elicit fundamental information such as age of the patient, the acuity of onset, pain location and pattern of radiation, duration of headache, frequency and severity of attacks, nature of the pain and many other questions related to family history [5].

To exclude secondary causes of headache, particularly when patients are presenting with new onset headache or with sudden changes in the headache pattern, it is important to consider the "red flags" signs to decide whether the patient could be having a serious condition that requires further investigation. Red flags act as a decision threshold to help with identifying headache patients who would benefit from having a prompt brain imaging [25].

Examples of red flags include; new onset or change in pattern of headache in patients who are aged less than 10 years or over 50 years, new onset of headache in patients with a history of cancer or HIV. Other example of red flags are when headache changes with postural changes, presence of fever, weight loss or abnormal blood tests, and many other signs [4, 5, 24, 25]. The table below summarises the differences between primary and secondary headaches in a very simple way.

Table 2-1: The difference between the primary and secondary headache

	Primary headache	**Secondary headache**
Prevalence	More common	Less common
Age of patient	Between 10 and 50 years of age.	Younger than 10 years Older than 50 years
Onset	More than 6 months	Sudden onset
Pathological causes	Problem with brain function	Problem with brain structure
Diagnosis	Based on symptoms Usually normal examination normal imaging test No neurological sign	Based on aetiology Abnormal examination Abnormal imaging test Neurological signs (i.e. abnormal gait, speech and confusion). Systemic sign (i.e. fever and weight loss).
Prognosis	Headache history with no change in pattern.	Progressive pattern.
Family history	Positive history, particularly for migraine	Negative family history

2.3. Primary headache disorders

Primary headache disorders are the most common in the community, they are not related to any underlying medical condition and the headache itself is the disorder [4]. In contrast, secondary headache disorders occur secondarily to another medical condition; some of which may be life threatening and therefore require quick and accurate diagnosis. Secondary headache is extremely rare and represents less than 1% of the population who experience headaches [26].

Brain imaging is important for optimal management of brain tumours as well as for other secondary headache disorders, in particular with the presence of red flag signs, nevertheless it is not really recommended for the clinical management of the majority of headache disorders. In contrast, brain imaging is usually ineffective for the diagnosis of most primary headaches such as migraine and tension-type headache [7]. The most common major categories of primary headache will be reviewed in sequence with the subsections below. This section presents an overview of the main types of primary headache disorders along with their clinical signs and symptoms according to the operational diagnostic criteria that were formulated by IHS [3], an overall comparison of these main types is also presented in this chapter.

2.3.1. Migraine

Migraine is the commonest debilitating and disabling primary headache disorder. Including both Chronic Migraine (CM) and Episodic Migraine (EM) forms, it affects up to 18% of women, less frequently in men [20, 27]. According to ICHD-3, two major subgroups of migraine can be distinguished based on the presence or absence of aura, which is a focal neurological phenomenon that often precedes the headache [3, 4]. Migraine without aura can be defined as a recurrent headache with moderate or severe intensity that last 4-72 hours. Typical characteristics of migraine are unilateral location, pulsating quality, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia [3].

Patients could meet the criteria of migraine without aura by different combinations of features; no single feature is essential to be present. Because two of four pain features are required, therefore a patient with unilateral, throbbing pain could be eligible to meet the criteria, so does a patient with moderate pain that is aggravated by physical activity. Likewise, only one of two possible related symptom

combinations is required. Patients with nausea or vomiting, but without photophobia or phonophobia meet the conditions, as do patients with photophobia and phonophobia but without nausea or vomiting [23]. According to the criteria of IHS, migraine without aura can be defined as a clinical syndrome recognised by headache with certain features and involved symptoms as shown in table 3-2.

Table 2-2: Migraine without aura

A	**At least 5 attacks fulfilling criteria B-D**
B	Headache duration of 4 to 72 hours (For untreated or unsuccessfully treated).
C	Headache has at least two of the following characteristics 1. Unilateral location. 2. Pulsating quality (e.g., varying with the heartbeat). 3. Moderate or severe pain intensity. 4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D	During headache at least one of the following 1. Nausea and/or vomiting. 2. Photophobia and phonophobia.
E	Not attributed to another disorder Secondary causes of headache must be excluded (Normal exam, imaging, etc.)

On the other hand, migraine with aura is primarily recognised by the focal neurological phenomena that often precede the headache, however, in some cases it comes with or occurs in the absence of the headache [3, 4, 23]. Migraine with aura affects approximately one third of migraine patients [26]. Migraine with typical aura is the commonest form of migraine with aura [23]. Typical aura includes visual and/or sensory and/or a speech symptom, however, visual aura is the most common form. Most aura symptoms are progressive and develop gradually from 5 to 60 minutes prior to the headache (and usually around 20 minutes) [3, 26].

Visual aura usually includes transient hemianopia disturbance or a spreading scintillating scotoma [26]. Sometimes visual symptoms appear jointly or in sequence with other reversible focal neurological disturbances like unilateral paraesthesia of hand, arm or even face and/or dysphasia, all indications of functional cortical disturbance of one cerebral hemisphere [26]. Table 3.3 presents the diagnosis criteria of migraine with typical aura in accordance with the criteria of IHS.

Table 2-3: Migraine with typical aura

A	**At least two attacks fulfilling criteria B-D**
B	Aura consisting of at least one of the following, but no motor weakness: 1. Fully reversible visual symptoms including positive features (e.g., flickering lights, spots, or lines) and/or negative feature (i.e., loss of vision) 2. Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness) 3. Fully reversible dysphasic speech disturbance[3][3][3][3][3][3].
C	At least two of the following: 1. Homonymous visual symptoms and/or unilateral sensory symptoms. 2. At least one aura symptom develops gradually over 5 minutes and/or different aura symptoms occur in succession over 5 minutes. 3. Each symptom lasts ≥ 5 and ≤ 60 minutes.
D	Headache that meets criteria B-D for migraine without aura (i.e. table 3-2) begins during the aura or follows the aura within 60 minutes.
E	Symptoms not attributed to another disorder.

Several studies have shown that, patients with CM reveal a greater personal and societal burden, as well as impaired quality of life because they are considerably more disabled compared to patients with EM [27]. The study of American Migraine Prevalence and Prevention (AMPP) has used different tests to assess headache impact on the lives of patients with migraine; the Headache Impact Test (HIT-6) results have revealed that patients with CM were substantially more likely to experience severe headache impact (72.9%) in comparison with those with EM (42.3%). Moreover, the Migraine Disability Assessment (MIDAS) test outcomes have similarly showed that patients with CM had a greater disability, where a disability evaluation on the MIDAS test depends on the disability score, which is derived from decreased productivity such as missed days of work and school [28]. Migraine is classified as EM when headache attacks a patient for 14 or fewer days per month, otherwise CM is considered [3, 4].

2.3.2. Tension-type headache

Tension-type headache (TTH) is a very common form of primary headache [23], with a lifetime prevalence ranging from 30 to 78% in the general population as shown by several studies [3, 22]. According to the criteria of IHS, the diagnostic

criteria for tension-type headache have primarily been designed to differentiate between tension type headache and migraine [3]. In contrast to migraine, the main pain features of tension-type headache can be represented by the absence of migraine's characteristic features. The pain is mild to moderate and not as severe as in migraine, non-throbbing quality, not aggravated by physical activity. No nausea or vomiting is associated, although no more than one of phonophobia or photophobia [4, 20, 23, 29]. The headache can be unilateral, but is commonly generalised. It can be described as pressure or tightness, such as a tight band around the head, and usually arises from or spreads into the neck [26].

The underlying cause of TTH is doubtful, but the most likely contributing factor for episodes of infrequent TTH is probably the activation of hyperexcitable peripheral afferent neurons from head and neck muscle [30]. Although muscle tenderness and psychological tension is not evidently the cause of TTH, however they are usually associated with it and worsen the pain. Both migraine and TTH have chronic forms, and sometimes it can be difficult to differentiate between them, in particular when migraine or TTH is invoked by neck problems.

Most of the migraine's features explicitly differentiate this type of headache from TTH, and therefore help in a precise diagnosis. Similar to episodic TTH, migraine is a recurrent headache that can last from a couple of hours to a few days. However, while TTH is commonly generalised, migraine pain is mostly unilateral; and while migraine has a pulsating quality with moderate-to-severe pain, TTH presents as a mild-to-moderate in intensity and a dull ache or feeling of a tight band around the head [30, 31]. Furthermore, patients with TTH headache are significantly less disabled than patients with migraine or cluster headache [23]. A headache diary can help to distinguish between migraine, TTH, and other primary headaches [30].

The ICHD-3 beta differentiates three subtypes of TTH: infrequent episodic TTH, which occurs on less than one day a month (on average less than 12 days per year). Frequent episodic TTH, that occurs on less than 15 days a month for at least three months and a chronic TTH, which occurs for more than 15 days a month (on average more than 180 days per year) [3, 22, 29].

Table 2-4: Tension-type headache

A	**At least 10 episodes fulfilling criteria B–E** **(Infrequent episodic, headache < 1 day/month),** **(Frequent episodic, 1–14 days/month), or** **(Chronic ≥ 15 days/month).**
B	Headache lasting from 30 min to 7 days
C	Headache has at least two of the following pain characteristics 1. Pressing or tightening (non-pulsating) quality. 2. Mild or moderate intensity (may inhibit but does not prohibit activities). 3. Bilateral location. 4. No aggravation by walking stairs or similar routine physical activity
D	Both of the following 1. No nausea or vomiting (anorexia may occur). 2. Photophobia and phonophobia are absent, or one but not the other may be present.
E	Not attributed to another disorder

2.3.3. Trigeminal Autonomic Cephalalgias (TACs)

The trigeminal autonomic cephalalgias (TACs) are another group of primary headache disorders that were first proposed by Goadsby and Lipton and listed in ICHD-3 under their own section [32]. TACs are rare in comparison with other primary headache disorders such as migraine and TTH. They can be characterised by a relatively short duration of attacks with severe unilateral pain associated with autonomic dysfunction ipsilateral [4, 23, 33].

3.3.3.1 Cluster headache

Cluster headache (CH) is the commonest form of the TACs. CH predominantly appears in young adulthood as early as the second decade of age; persist well in life, even in the seventh decade [34]. CH is extremely rare in children, men are also more than three times more likely to be diagnosed with this type of headache , and it is quite often in smokers [23, 35]. CH is usually severe, recurring, but generally briefer than migraine and non-throbbing [3]. The pain is excruciatingly severe, intense, strictly unilateral, and variously described as sharp, drilling and stabbing [23]. It is most often located behind one eye, and sometimes generalised to a larger area of the head [26]. In general, the pain takes 10-15 minutes to reach its peak intensity and

remains excruciatingly intense for an average of one hour, and usually ranges from 15 to 180 minutes. Typically, it occurs at the same time every day, most often at night, 1-2 hours after sleep [23, 26]. Patients during the attack find it difficult to lie down, because it aggravates the pain, and can cause themselves harm through beating their head on the wall or floor until the pain reduces, usually after 30-60 minutes [23, 26].

CH typically attacks for 6-12 weeks, occurring once every year or two years and usually at the same time each year [26]. CH is usually accompanied by swollen or drooping eyelid, teary or red eye, pupil contraction in one eye, stuffy or runny nostril, sweaty face and forehead and a sense of restlessness and agitation. The presence, at least, of one or two of the associated symptoms can secure the diagnosis [23, 26]. ICHD-3 has divided CH in two forms. The episodic CH attack cycle occurs in periods lasting from 7 days to 1 year, separated by remission periods of a month or longer each year. Approximately 85% of patients affected by cluster headache have the episodic form. The remaining 15% of cluster sufferers have the chronic form of CH. They will have a daily or near-daily headache for more than 1 year, and it will be without remissions or with remissions that last less than a month in a given year. Generally, 5% of the chronic form evolves from the episodic form (secondary chronic form), or it may start de novo as a primary chronic cluster in 10% [3, 23, 34]. Table 3-5 displays the diagnostic criteria for CH according to the guidelines of IHS.

Table 2-5: Cluster headache

A	**At least five attacks fulfilling criteria B–D**
B	Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes untreated.
C	Headache accompanied by at least one of the following symptoms or signs that have to be present on the side of the pain: 1. Conjunctival injection, lachrymation, or both. 2. Nasal congestion, rhinorrhoea, or both. 3. Eyelid oedema. 4. Forehead and facial sweating. 5. Miosis, ptosis, or both. 6. A sense of restlessness and agitation.
D	Frequency of attacks: from one every other day to eight per day for more than half of the period (or time if chronic).
E	Not attributed to another disorder.

Episodic cluster headache:

At least two cluster periods lasting 7 days to 1 year, separated by pain-free periods lasting ≥ 1 month.

Chronic cluster headache:

Attacks occur for > 1 year without remission or with remission for < 1 month.

3.3.3.2 Paroxysmal hemicrania

In 1974, Sjaastad and Dale first identified Paroxysmal hemicrania (PH) [36]. It is a rare primary headache disorder belonging to TACs [37]. PH is characterised by relatively short attacks of severe, strictly unilateral pain that is orbital, supraorbital, and temporal or in any combination of these sites. The attack duration is 2-30 minutes and occurs several times a day [3], and the typical frequency is more than five attacks per day, however there are reports of 1 to 40 attacks per day [35]. The attacks are associated with at least one autonomic symptom on the same side of the pain such as ipsilateral conjunctival injection and tearing with nasal congestion and rhinorrhoea. The syndrome is also characterised by its absolute response to therapeutic doses of indomethacin [3, 35, 37]. Similar to CH, HIS guidelines describe a chronic and episodic form of PH. Episodic PH occurs in periods lasting from 7 days to 1 year, separated by pain-free periods lasting at least 1 month, while chronic PH occurs for more than 1 year and without pain-free period, or with pain-free periods lasting less than 1 month [3].

3.3.3.3 SUNCT

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) is among the rarest primary headache syndromes. ICHD-3 identifies SUNCT as a short-lasting unilateral pain that is stabbing or throbbing. The pain is moderate to severe; however, it considered being less severe pain compared to other TACs such as CH and PH [3]. The paroxysms of pain is lasting for 1-600 seconds, but commonly last between 5 and 250 seconds and occurring as single stab, series of stabs or in a saw-tooth pattern. Patients can have 20-300 attacks per day [35]. The frequency of attacks may be different between episodes. Some patient can have up to 30 episodes per hour, while it is more common to have 5-6 episodes per hour. The most prominent autonomic feature of SUNCT is conjunctival injection.

Migraine's characteristic features such as nausea, photophobia and phonophobia might occur in SUNCT and other TACs for patients who had a personal or family history of migraine in a first-degree relative [38].

The most significant clinical indication pointing toward SUNCT and against trigeminal neuralgia is the prominent distribution of pain in the ophthalmic division of the trigeminal nerve. Moreover, the attacks could be triggered by various cutaneous stimuli such as touching the face, brushing teeth and shaving [3, 35]. Despite the distinctive clinical differences such as the frequency and duration of attacks, SUNCT shared many of its basic features with CH and PH such as episodic attacks, unilateral pain and autonomic symptoms. However, unlike PH, SUNCT is not affected by therapeutic doses of indomethacin, and in contrast to CH, there is no significant effect of using oxygen, sumatriptan or verapamil [35].

2.4. Presentation and comparison

Primary headaches represent more than 90% of headache complaints presented to GPs. Although primary headaches are the most common, they are not serious or life threatening. There are no distinguishable causes for primary headaches, and the diagnosis is most often made by the history of headache as well as the associated signs and symptoms. Primary headaches may share certain features; pain is severe for migraine and CH as an example. However, CH varies from migraine primarily in its pattern of occurrence. CH is in briefer episodes over a period of weeks or months. Sometimes, a whole year can pass between two CHs. Migraine usually does not follow this type of pattern. Consequently, and after a comprehensive study of the literature of primary headaches, we decided to conclude this chapter with a thorough comparison of the major types of primary headache disorders. Although there are some intertwined features between them, such a comparison provides significant support in distinguishing a particular type of headache from another.

Table 2-6: Comparison of migraine, tension-type and TACs

	Migraine	Tension-type headache	Cluster headache	Paroxysmal hemicrania	SUNCT
Gender ratio (M:F)	3:1	5:4	3:1	1:3	**1:1.8**
Age of onset	15-55 years	25-30 years	28-30 years	20-40 years	**20-50 years**
Prevalence	18% F - 6% M	30 up to 78%	0.9%	0.02%	**Very rare**
Pain features					
Quality	Throbbing	Tightening	Boring, sharp, burning	Boring	**Stabbing**
Intensity	Moderate to severe	Mild to moderate	Severe to very severe	Severe	**Moderate to severe**
Location	Unilateral	Bilateral	Unilateral	Unilateral	**Unilateral**
Duration of attack	4-72 hours	30 min to 7 days	15-180 min	2-30 min	**1-600 sec**
Symptoms					
Nausea	++	--	≈	≈	≈
Vomiting	++	--	±	±	±
Photophobia	++	++	≈	≈	≈
Phonophobia	++	++	≈	≈	≈
Aura symptoms	≈	--	--	--	--
Autonomic dysfunction	--	--	++	++	++
Triggers					
Physical activity	++	--	--	±	±
Laying down or sleep	--	--	++	--	--
Alcohol	++	±	++	≈	--
Cutaneous stimuli	--	--	--	--	++
Stress	±	++	--	++	±
Relaxation after stress	--	--	--	++	--
Exercise	±	--	--	++	≈
Neck movement	--	--	--	++	++

Symbols: ++ positive; -- negative; ± probable; ≈ rare.

The table has been drawn based on the following sources [3, 35, 38-40].

2.5. Secondary headache disorders

There is a definite underlying cause of secondary headaches that identifiable on examination or investigation. Secondary headaches are very rare in comparison to primary headaches; however, they are convoluted because they can lead to serious complications. Secondary headache is a symptom of another disease that can activate the pain-sensitive nerves of the head. Secondary headache has numerous causes including head and neck trauma or injury; intracranial vascular disorders such as ischaemic stroke, or non-vascular disorders such as high cerebrospinal fluid (CSF) pressure (i.e. hydrocephalus), infection and psychiatric disorder, and disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure [2-4, 22].

Headache attributed to idiopathic intracranial hypertension (IIH) or hydrocephalus is an example of secondary headache. It was initially described in 1897 as a syndrome of papilledema and elevated intracranial pressure attributed to impaired cerebrospinal fluid (CSF) flow. Hydrocephalus is a neurological condition in which the cerebrospinal fluid (CSF) is excessively accumulated around the brain, which can lead to an enlargement of the ventricular system of the brain and increase the pressure inside the head. It is caused by various etiological factors, however the common final result is insufficient passage of cerebrospinal fluid (CSF) from its point of production in the cerebral ventricles to its point of absorption into the systemic circulation [41].

This excessive build-up of CSF yields a harmful pressure on the tissues of the brain. In an adult human, there is approximately 150 cubic cm of CSF surrounds the brain, the spinal cord and present in the ventricular system within the brain. The CSF possesses many functional benefits such as protecting from mechanical stresses by minimising the pressure inside the cranial vault induced brain expansion during cardiac constriction. It is also supporting the brain weight by the buoyancy. CSF protects the brain and spinal cord from shocks by acting as a cushion. Moreover CSF plays an important role in the absorption and carrying away of the toxic by-products of metabolism [42].

2.6. Chapter summary

In this chapter, we have reviewed and understood the main types of primary headaches including migraine, tension-type headache and TACs. Each of them presented with its clinical features and diagnostic criteria based on the latest clinical guidelines and references. This deep investigation of headache causes and patterns leads to a comprehensive comparison that can highlight common and different qualities of primary headaches. In general, it can be noted that the criteria of IHS is the most agreed clinical guideline worldwide that is in use for clinical diagnosis of headache disorders. These criteria also extensively used to establish almost all of the diagnostic support modules.

CHAPTER 3: LITERATURE REVIEW

3.1. Introduction

Over the last decades, information technology in general and artificial intelligence in particular have gradually involved in every single field of life, starting from industry, business, weather forecasting and media, but the most significant development has taken place in the field of healthcare. Healthcare organisations are continually endeavouring to improve patient care and provide better services. Introducing information technology into healthcare delivery is expected to become an enabler to get more efficient and effective healthcare services. Under the term of electronic health (e-health), information and communication technology has changed the means of patient care by providing home healthcare services with better infrastructure, cost effectiveness and quality of services [43].

Currently, healthcare applications have expanded from (e-health) to mobile health (m-health). The main driving force behind the change was the wide acceptance and usage of smartphone mobile devices worldwide and a suitable platform and environment for healthcare applications provided by these devices [44, 45]. This chapter reviews the literature to investigate recent studies and decision support systems (DSS) that target the diagnosis of primary headache disorders. This chapter also compares and evaluates these relevant studies to explore their advantages and drawbacks, which enable us to create a new diagnostic model that overcomes current difficulties.

3.2. Intelligent driven modules to diagnose headaches

The development of clinical DSS to diagnose primary headache disorders has become an interesting research topic, especially after the launch of the IHS clinical criteria for the classification of headaches. A range of studies or diagnostic models have been proposed or already developed to aid headache specialists in making decisions with respect to the diagnosis of headaches. Many others were restricted for patients' usage such as an application to enable patients in keeping track of their conditions and treatments or applications to get recommendations from health

professionals. This section reviews the most recent studies that have been published over the last decade.

3.2.1. Neurologist expert system (NES)

It is a rule-based DSS developed by Al-Hajji [46] to diagnose more than ten types of neurological diseases including migraine and cluster headache. In this DSS, knowledge has been obtained from different sources such as domain experts, specialised databases, books and a few electronic websites. A list of neurological diseases has been stored in a table and approximately 70 related symptoms were also stored in another table. Then, a combination between each neurological disease and its most related symptoms has been derived.

In fact, the diagnosis of many neurological diseases disease, such as Alzheimer's, Parkinson's, Epilepsy, in addition to migraine and cluster headache, can be challenging even for neurology specialists themselves. It is a wide range of diseases that generally have shared symptoms and various diagnostic procedures. For example, brain imaging can play a vital role in the diagnosis of Alzheimer's or the early detection of Parkinson's disease. Moreover, there was no clear adoption of IHS criteria with respect to the diagnosis of migraine and cluster headache. Therefore, using a very simple link between each neurological disease and its symptoms cannot be seen as an effective clinical DSS and would bear a large error rate.

3.2.2. Expert system based headache solution (ESHS)

An expert system was proposed by Hasan and his partners [47] to diagnose different types of headache based on expert knowledge. ESHS includes a set of key questions that derived from neurology experts to help other doctors when diagnosing patients with headache. When symptoms are entered in accordance with these questions, ESHS then would help in detecting the type of headache and generate prescriptions. This expert system uses very simple yes/no questions derived from expert's knowledge instead of the globally agreed criteria of IHS. Moreover, the authors failed to clarify who those experts are, and show their affiliations and experiences.

3.2.3. A guideline-based DSS for headache diagnosis

A computerised headache guideline method was proposed by Yin and others [48] to assist general practitioners in primary hospitals to improve the diagnostic accuracy of primary headaches such as migraine, tension-type headache and cluster headache. The main aim was to develop a system to counteract the complexity of the second version of IHS criteria. Authors pass through three main steps to develop their clinical DSS. A clinical specialist summarises the diagnostic guidelines of IHS and expresses them as a flowchart in the first step. Then, a knowledge engineer establishes a computerised model for headache knowledge representation based on these flowcharts. Finally, the knowledge representation model is translated into a series of conditional rules, which are used by the inference engine. This clinical DSS evaluated by 282 previously diagnosed headache cases obtained from a Chinese hospital.

3.2.4. Validation of a guideline-based DSS for headache diagnosis

In 2014, Dong and his colleagues have developed a guideline-based clinical DSS for headache diagnosis [49]. They have followed the same procedure presented in [48] for knowledge acquisition, but using the third version of IHS criteria and validated their system by 543 data sheet of patients with headache obtained from the International Headache Centre at the Chinese PLA General hospital, Beijing, China. The main difference between this guideline-based DSS and the guideline-based DSS developed by Yin in [48] is that three more types of headache have been added to the library of this DSS including probable migraine, probable tension-type headache, new daily persistent headache and medication overuse headache. As shown in [49], there was some improvement in the diagnosis in comparison with DSS by Yin in [48].

3.2.5. Case-based reasoning DSS for headache diagnosis

A computer-aided diagnosis method was proposed by Yin et al. [50] and employs case-based reasoning (CBR) method to differentiate between probable migraine and probable tension-type headache. This CBR clinical DSS provides recommendations to the general practitioners based on the previously solved cases in the built-in library. This library contains 676 data sheets of patients with probable migraine and

probable tension-type headache that were collected by clinical interview. Each data sheet consists of 74 different attributes including patients' information and medical history in addition to headache symptoms derived from the IHS criteria. The authors employ genetic algorithm (GA) to assign weights to these attributes and K-nearest neighbour (KNN) method to measure the similarity between new headache cases and the previous cases in the library.

3.2.6. Hybrid intelligent reasoning DSS

A hybrid DSS tool was proposed by Yin and his partners [51] using a combination of rule-based and case-based reasoning methods to improve the diagnosis of primary headache disorders such as migraine, tension-type headache and cluster headache. The reasoning modules in this clinical DSS run independently, the rule-based module is the first diagnostic module and the case-based module is the second. The diagnostic rules are summarised by a clinical specialist based on the criteria of IHS in the first module, while data sheets of previous headache cases have been used in the second module. The diagnostic procedure starts through applying the first diagnostic module to a new headache case, if headache symptoms are typical and match the existing rules, then a diagnostic decision can be made. Otherwise, the headache case is transferred to the case-based module to search for the most similar previous cases.

The research group in [50] claim that the CBR clinical DSS shows an improvement with respect to the diagnosis of primary headaches when compared to their previous works [48, 49] that were built around the guideline-based concept. Although the core concept of [48, 49] and [50] seems to be similar, however knowledge acquisition methods are completely different. In [48, 49], the specialist derives diagnostic guidelines from IHS criteria, which is then expressed as a set of conditional rules, while [50] uses clinical interviews of patients with headache as a knowledge acquisition stage. The same research group have also proposed a hybrid clinical DSS in [51], which is a merger of their previous proposals in [48, 49] and [50].

3.2.7. Automatic DSS for the classification of primary headaches

This is a machine learning based DSS proposed by Krawczyk and his colleagues [52] to support the classification of primary headaches. The main aim of this study was to

distinguish between the episodic tension-type headache and migraine without aura. Authors have prepared a questionnaire according to the second version of the criteria of IHS as a knowledge acquisition stage. The questionnaire includes general information of patients such as age, gender, marital status, level of education, etc., in addition to questions that related to headache characteristics such as frequency of attacks, quality of pain, associated symptoms, headache location, intensity and triggers. Six machine-learning algorithms were applied to the collected data including Naïve Bayes, Decision Tree (C4.5), Support Vector Machine, Bagging, Boosting and Random Forest. Using the 10-fold cross validation method, the experiment showed that the best result could be achieved through a combination of Random Forest method with Bagging and/or Boosting methods.

3.2.8. Other headache diagnostic modules

Simić and others in [53] and [54] have proposed a computer-assisted diagnosis of primary headaches. It is a rule-based fuzzy logic (RBFL) system designed to help physicians when diagnosing patients with primary headaches such as migraine, tension-type headache and cluster headache. This work involves under the type of knowledge-based DSS, in which the criteria of IHS are expressed as a collection of IF-THEN statements. Another group of researchers in [55] trained artificial neural networks to diagnose migraine, tension-type headache and medication overuse headache. The artificial neural networks have been trained using questionnaire-based data collected from patients with headache.

Ufuk and others in [56] have evaluated an immune algorithm for the classification of migraine, tension-type headache and cluster headache. A website based survey expert system was used to collect data of patients with primary headaches. They conclude that the immune algorithm can help the neurologist with respect to the classification of primary headaches.

Eslami and his partners in [57] have designed a computerised expert system to help in the diagnosis of primary headache disorders such as migraine, tension-type headache, cluster headache and other trigeminal autonomic cephalalgias. A questionnaire was designed to approach all criteria of primary headache disorders based on the second version of IHS criteria. When a patient starts filling in the questionnaire, the expert system uses a simple human-like algorithmic reasoning to

classify the type of headache. Similarly, Maizels and Wolfe in [58] employ a simple human-like branching logic to determine the most appropriate diagnostic questions to ask the patients, then, classify the type of headache using modified Silberstein Lipton criteria and IHS criteria. Maizels and Wolfe implemented their expert system as a web-based tool with an interview section that includes questions about headache characteristics. The modified Silberstein Lipton criteria are used to classify patient with frequent headache, while IHS criteria are used to diagnose patients with brief headache syndromes.

Zafar and others in [59] proposed a clinical DSS to aid physicians in the diagnosis of migraine and other headaches and at the same time to enable patients living in remote areas to have medical check-ups. Zafar implemented his work as a web-based tool, in which information related to primary and secondary headaches are stored in the knowledge base. The inference engine will search this knowledge base to find suitable diagnostic recommendations based on headache characteristics. This proposed system, in fact, is considered as a black box because there is no clear sequence of operations in particular for knowledge acquisition.

3.3. Evaluation and justifications

Decisions taken made by headache specialists usually depend on clinical guidance, medical evidence, instructions and principles derived from medical science. In an ideal situation, clinical DSS should improve the use of knowledge to support those specialists in making more accurate decisions, and therefore enhancing the quality of care being delivered to the patient. Although clinical DSS have a potential to improve decision making, handling large amount of information and analysing real-time data or patient history, however, the use of clinical DSS is not yet widespread in clinics or hospitals. This might be because the majority of such systems are developed apart from healthcare professionals and there is lack of criteria for a proper use of intelligent methods in these clinical DSS [60].

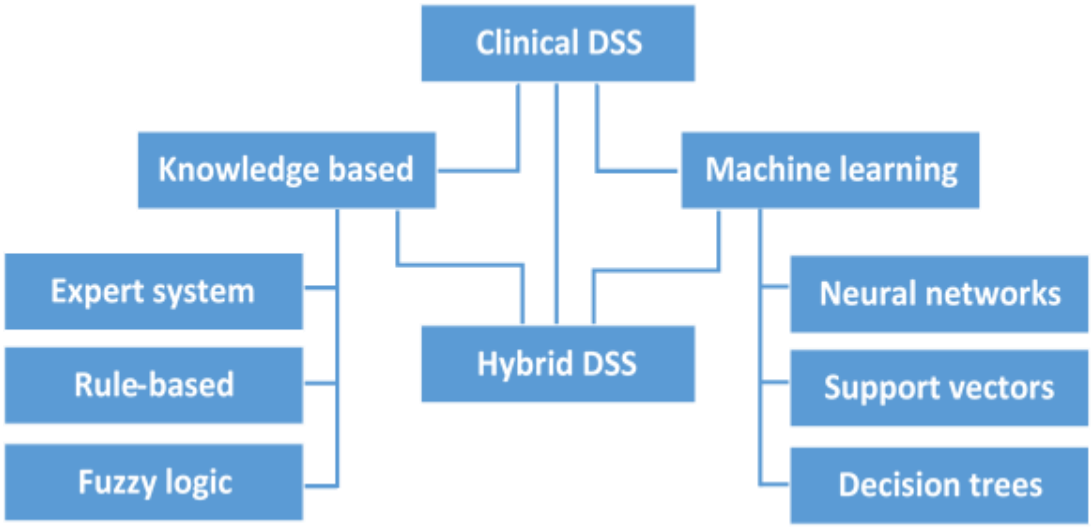


Figure 3-1: Types of clinical decision support systems

In general, we can categorise clinical decision support systems into three main groups as shown in figure 2-1. Knowledge-based clinical DSS is the first, machine learning based clinical DSS is the second, and hybrid clinical DSS that is based on a combination of the first two groups. The Knowledge-based DSS is designed and structured around the logic of IF-THEN statements, in which clinical guidelines such as IHS criteria or experts' knowledge are formed into rules and expressed by a computer engineer as a set of IF-THEN-ELSE statements. This usually includes a significant amount of information regarding the types of headache together with their signs and symptoms. Once the patient data are input, the inference engine examines the data against these IF-THEN statements to limit the outcome response.

A simple example of using knowledge based DSS presented in [61], in which the DSS includes a probable list of haematological diseases combined with their symptoms. Inputs to this CBC clinical DSS include patient information such as age, gender, altitude, pregnancy period in addition to the complete blood count (CBC) test result. The inference engine will suggest a list of probable haematological diseases based on these inputs. Although it is unable to provide an ultimate diagnosis, however, it is a good start for further and more disease-specific tests to confirm the diagnosis.

Going back to the diagnostic modules that are summarised in table 2-1, the core concept of the majority of them was approximately similar regarding the knowledge acquisition, where the international classification of headache disorders was used as

a base for deriving the diagnostic rules. These rules were summarised and expressed by a computer engineer. This style is commonly known as a rule-based method, by which the rules are formulated based on a human expert. The basic principle of the rule-based technique is pattern identification followed by a recommendation of what should be done in response. These rules are a conditional statement that links the supplied conditions to actions or results. Ideally, the rule is straightforward, understandable and represents the knowledge in near-linguistic form [60].

Table 3-1: Summary of diagnostic modules

No.	Authors	Year	Type of module	Knowledge	Type of headache
1	Al-Hajji [46]	2012	Knowledge-based	Domain experts	MIGR and cluster headache
2	Hasan et al. [47]	2012	Knowledge-based	Domain experts	Primary headaches
3	Yin et al. [48]	2013	Knowledge-based	IHS criteria	Primary headaches
4	Dong et al. [49]	2014	Knowledge-based	IHS criteria	Primary headaches
5	Yin et al. [50]	2015	Knowledge-based	Case-based similarity	Probable MIGR and probable TTH
6	Yin et al. [51]	2014	Knowledge-based	Case-based and IHS criteria	Primary headaches
7	Krawczyk et al. [52]	2013	Machine learning	IHS criteria	Episodic TTH and MIGR without aura
8	Simić et al. [53, 54]	2008	Knowledge-based	IHS criteria	Primary headaches
9	Mendes et al. [55]	2010	Machine learning	Questionnaire	Primary headaches
10	Ufuk et al. [56]	2016	Knowledge-based	Survey data	Primary headaches
11	Eslami et al. [57]	2013	Knowledge-based	Questionnaire	Primary headaches
12	Maizels and Wolfe [58]	2008	Knowledge-based	Silberstein Lipton criteria and IHS criteria	Primary headaches
13	Zafar et al. [59]	2013	Knowledge-based	Unknown	Primary and secondary headaches

The rules-based system style can facilitate the separation of knowledge from processing, in addition to allowing incomplete or uncertain knowledge to be expressed and bounded. However, implementing this kind of system could possibly carry certain downsides. First, rule-based systems are not able to learn and modify their rules from experience or via identifying patterns in clinical data. Secondly, navigating the categorisations and relationships in a large rule-based system can be complicated and time consuming. Third and the most important point is that the necessary information needed to derive these diagnostic rules might consist of more variables than the human mind can accommodate. There is persuasive evidence to indicate that the human ability to discover and understand complicated configuration relationships could be limited [62].

Therefore, deriving and formulating these diagnostic rules, with the limited ability of human mind to manipulate a large quantity of information or variables in considering a complex subject such as IHS criteria, may lead to insufficient representation of knowledge and eventually a poor diagnostic model [60]. Moreover, we would like to pay attention to the fact that the IHS criteria are designed to provide a ground truth for headache specialists, where this classification of headaches provides clear distinct definitions describing many different types of headache. However, these types of headache may share signs and symptoms in real world scenario and they also my change over time, which makes the classification of primary headaches not as clear as black or white (i.e. as we show in the procedural classification function). This means that there is a grey area in between, which can affect the diagnostic performance, validity and reliability of decisions made by such CDSMs. In this context; we are adopting a completely different approach, in which several machine-learning classifiers were applied to diagnose primary headache disorders using anonymised real-world data records of patients with primary headaches.

3.4. Chapter summary

In this chapter, we reviewed the literature to explore studies and decision support systems (DSS) that target the diagnosis or classification of primary headache disorders. The majority of these studies or systems have followed a rule-based system style, in which a computer engineer formulates the diagnostic rules as a set of IF-THEN-ELSE statements based on clinical guideline or prepared questionnaire.

Although the rule-based system style is straightforward, understandable and can represent the knowledge in near-linguistic form, however, it bears many serious downsides such as the inability to learn and gain knowledge over time and maintaining categorisations and relationships in a large rule-based system can be complicated. Therefore, we will avoid such a style of diagnostic models via the implementation of machine learning methods.

CHAPTER 4: DATA PREPARATION

4.1. Introduction

Since the data is a building block of every information system, a first step in the application of machine learning is to examine the characteristics of the data, which is commonly known as a data processing stage. In general, there are two main types of data in scientific researches, quantitative and qualitative. Quantitative data are the data that express items of interest numerically and quantitative research involves examining causal relations, patterns and associations in such data using statistical methods [63]. In quantitative data, measurement units are often used to represent observations, for example patients' age measured in years, patients' height measured in meter or inches, duration of pain measured in minutes or hours, years of suffering and so on.

In contrast, qualitative data is typically descriptive and it represents numbers of cases, scenarios, events, experiences using data from observations or interviews. In quantitative research, the phenomena examined cannot be fully comprehended through quantification. For instance, how do patients describe their headache characteristics? Where is the location of pain? Did patients or any of first-degree relatives suffer from a particular chronic condition? Qualitative research involves examining answers to these types of questions for a particular condition in order to understand patients' experience [63].

This chapter describes the process of knowledge acquisition. It begins by describing the data set, and then emphasises all potential key concerns that ought to be addressed in the pre-classification stage. In this chapter, we identify and process outliers in data, then, handle missing data using multiple imputations, and we end this chapter by normalising the data using min-max normalisation method.

4.2. Data description

This study re-uses the data set in [64] for the following reasons; a) the dataset has been collected by headache specialists in three medical-academic centres in Turkey (i.e. School of Medicine - Mersin University, Medical Faculty - Istanbul University and Istanbul Education Hospital). These centres combine clinical care with scientific

research. b) It is high dimensional data with 65 dimensions, which covers a wide range of patients' information including medical history, family history and psychological conditions, where such dimensions have not been covered in previous studies. c) The data set involves patients with the most common primary headache disorders including migraine with and without aura, chronic and episodic tension-type headache, trigeminal autonomic cephalalgias TACs (i.e. cluster headache, paroxysmal hemicranias and SUNCT). This diversity of patients has not been addressed in previous studies as well. Finally, d) the data set was collected with the aim of identifying a new sub-group of patients with vestibular symptoms in primary headache disorders, where it is ideal for diagnostic purposes.

The data set consists of 832 records of patients with primary headache disorders, and each record involves 65 attributes, including class attribute, as shown in table 4-1. We can group patients' records into three main categories. The first category includes patients with tension-type headache. It is the largest group of patients and includes 383 records, which represents 46.03% of the data. Out of 383 records, 221 records are for patients with episodic tension-type headache and 162 records are for patients with chronic tension-type headache. The second category includes patients with migraine, which consists of 378 records. It constitutes 45.43% of data. More than two-thirds of the second group are for patients with migraine without aura, i.e. around 300 records. The remaining 78 records are for patients suffering from migraine with aura.

The last category of records is for patients with TACs, which comprises of 71 records and represents 8.54% of the data. These 71 records are distributed as follows; 53 records are for patients with cluster headache, 12 records are for patients with paroxysmal Hemicrania and six records for patients with SUNCT. The number of records for patients with TACs is considerably less than other records (i.e. patients with migraine and tension-type headache). It is naturally inherited because the occurrence of TACs is very rare in comparison with other primary headache disorders. However, this can lead to an imbalanced class distribution that may affect the learning approach. We will discuss and handle this issue further in the next chapter.

Table 4-1: Data attributes

No.	Data attributes	Level of measurements	Descriptions
1	Gender	Dichotomous	Male/Female
2	Age	Numerical	Calculated in years
3	Age of admission	Numerical	Calculated in years
4	Diagnosis	Categorical	Type of primary headache – Class attribute
5	Headache onset	Numerical	Calculated in months
6	Headache frequency	Numerical	Days per month
7	Headache characteristic	Categorical	Throbbing, Pressing, Dull, Stabbing, lightening
8	Headache duration	Numerical	Calculated in hours
9	Headache location	Categorical	Unilateral, Bilateral, Frontal, Periocular, Bi-temporal, Occipital, Calvarial
10	Headache intensity	Numerical	Visual analogue scales (VAS) 1-10
11	Accident	Dichotomous	Present/Absent
12	Periodic vomiting	Dichotomous	Present/Absent
13	Motion Sickness	Dichotomous	Present/Absent
14	Abdominal pain	Dichotomous	Present/Absent
15	Epilepsy	Dichotomous	Present/Absent
16	Surgery	Dichotomous	Present/Absent
17	Allergy	Dichotomous	Present/Absent
18	Homocysteinemia[1]	Dichotomous	Present/Absent
19	TIA/Stroke[2]	Dichotomous	Present/Absent
20	Atherosclerosis[3]	Dichotomous	Present/Absent
21	Hyperlipidaemias[4]	Dichotomous	Present/Absent
22	Oral contraceptive	Dichotomous	Present/Absent
23	Hypertension	Dichotomous	Present/Absent
24	Diabetes	Dichotomous	Present/Absent
25	Coronary Artery disease	Dichotomous	Present/Absent
26	Snoring	Dichotomous	Present/Absent
27	OSAS[5]	Dichotomous	Present/Absent
28	Infantile colic[6]	Dichotomous	Present/Absent
29	Medication overuse	Dichotomous	Present/Absent
30	Pain killer using frequency	Numerical	The frequent usage of painkiller per month.
31	Medication overuse duration	Numerical	Calculated in months
32	Headache	Dichotomous	Present/Absent
33	Hypertension	Dichotomous	Present/Absent
34	Atopic disorder[7]	Dichotomous	Present/Absent
35	Diabetes	Dichotomous	Present/Absent
36	Heart disease	Dichotomous	Present/Absent
37	Epilepsy	Dichotomous	Present/Absent
38	Psychopathology[8]	Dichotomous	Present/Absent
39	Smoking	Dichotomous	Yes/No
40	Smoking duration	Numerical	Calculated in years
41	Emotional stress	Dichotomous	Present/Absent
42	Physical activity	Dichotomous	Present/Absent
43	Menstrual cycle	Dichotomous	Present/Absent
44	Seasonal	Dichotomous	Present/Absent
45	Alcohol	Dichotomous	Present/Absent
46	Skipping meals	Dichotomous	Present/Absent
47	Positional association	Dichotomous	Present/Absent
48	Nausea	Dichotomous	Present/Absent
49	Vomiting	Dichotomous	Present/Absent
50	Phonophobia	Dichotomous	Present/Absent
51	Photophobia	Dichotomous	Present/Absent
52	Dizziness	Dichotomous	Present/Absent
53	Sleep disturbances	Dichotomous	Present/Absent

54	Vertigo	Dichotomous	Present/Absent
55	Osmophobia[9]	Dichotomous	Present/Absent
56	Allodynia[10]	Dichotomous	Present/Absent
57	Normal	Dichotomous	Present/Absent
58	Anxiety	Dichotomous	Present/Absent
59	Depression	Dichotomous	Present/Absent
60	Obsession	Dichotomous	Present/Absent
61	Psychosis	Dichotomous	Present/Absent
62	Fundoscopy	Dichotomous	Normal/Abnormal
63	Fundoscopy explanation	Numerical	Comments
64	Neurological examination	Dichotomous	Normal/Abnormal
65	Pericranial muscle tenderness	Dichotomous	Present/Absent

[1] Abnormally high levels of Homocysteine in the serum, above 15 µmol/L.

[2]A transient ischemic attack (TIA), also called a mini stroke, occurs when a blood clot blocks blood flow in the brain.

[3]A serious condition where arteries become narrow or clogged up by fatty substances known as plaques or atheroma.

[4]Elevated lipid levels in the blood.

[5]Obstructive Sleep Apnoea syndrome, a condition where the walls of the throat relax and narrow during sleep, interrupting normal breathing.

[6]Distress or crying in an infant, which lasts for more than three hours a day, for more than three days a week, for at least three weeks in an otherwise healthy infant.

[7]The genetic tendency toward developing a classical allergic diseases including; atopic dermatitis, allergic rhinitis, and asthma.

[8]A study of mental disorders.

[9]Refers to a fear, aversion or psychological hypersensitivity to odours.

[10]An abnormal sensation, in which patients feel pain from something that shouldn't be painful.

[11]Also called Ophthalmoscopy, is a test that allows a doctor to see inside the back of the patient's eye and other structures using a magnifying instrument and a light source.

Headache data set includes a combination of quantitative and qualitative data described using different levels of measurement, such as numerical, dichotomous and categorical. Although the levels of measurement differ in many ways, they are unifying both quantitative and qualitative data into four different levels of measurement or scales [65]. Categorical and dichotomous scales are within the scope of qualitative attributes, numerical scales are belonging to quantitative attributes [66]. These categories convey a different amount of information. In fact, measurement is the method of assigning numbers or labels to items of interest in order to make the data amenable to statistical analysis and machine learning requirements [65]. However, the majority of machine learning algorithms are merely supporting numerical attributes, which require converting nominal attributes into a format that could be supported by these learning algorithms. In other words, providing the data in a numerical representation. Therefore, the categorical and dichotomous variables were dummy coded. For example, the absence of a certain condition was coded as zero; in contrast, the presence of that condition was coded as one.

4.3. Outliers' detection

Outliers are strange data points that are distant from other members of a given data cluster [67]. In general, outliers may arise from procedural error, such as inaccurate data collection, or they can be inherited from the natural variance of the data. Osborne and Amy [68] have described a number of other causes that may lead to outliers, while Zhao [69] identifies many different methods to detect outliers including visual inspection via plots, clustering and local outlier factor.

This study follows the visual inspection manner and uses box and whisker plot (usually known as boxplot) to detect outliers. Boxplot is a straightforward way that graphically depicts clusters of data points via their quartiles. Boxplot employs median and interquartile range IQR to detect the outliers, where the median is the middle number of an ordered set of numbers and the interquartile range is the variance between the first and third quartiles. In the boxplot, outliers are the data points that are located beyond the extremes of the whiskers [69]. To be more precise, outliers are the data points that fall above $\mathrm{Q3} + 1.5(\mathrm{IQR})$ and below $\mathrm{Q1} - 1.5(\mathrm{IQR})$, where Q1 is the first quartile, Q3 is the third quartile, and $\mathrm{IQR} = \mathrm{Q3} - \mathrm{Q1}$.

This section plots the data variables in accordance with the types of headache to assist in determining the outliers for each group of patients separately. This is mainly because different types of headache have different ages of onset, features, durations and intensity. Therefore, plotting variables with three major types of headache as a bunch would lead to inaccurate identification of outliers. Figure 4-1 shows the outliers within continuous variables, i.e. quantitative attributes, where circles represent outliers while stars refer to extreme outliers. The Box plot displays outliers and extreme outliers with their record numbers.

Outliers are usually handled in one of three methods. First, retain the outliers and handle them just like every other data point. Second, trimming them (i.e. remove outliers from the sample) and third, winsorising them [70]. Retaining outliers and handling them just like every other data point may overvalue them and lead to estimates that significantly vary from the legitimate population value. Trimming outliers is a very common practice in the literature; however, it may not be an appropriate way when the outliers are legitimate values [71]. The trimming method assumes that outliers are due to mistakes. For example, the measurement of a given

variable could be entered as 10000 instead of 100.00, which can cause a huge change in the estimates. Therefore, this method is usually recommended for outliers due to typographical mistakes or measurement errors. Furthermore, trimming outliers is generally unacceptable because they can be legitimate observations and may signify the natural variance of data. On the other hand, winsorising is a common procedure to handle outliers via modifying them to the next highest or lowest values within the distribution that are not suspected to be outlier [72]. Winsorising is recommended when the outliers are valid data points, i.e. legitimate observations [70].

There are controversies regarding the decision to keep or remove outliers, where there is no definitive answer to the problem. Some researchers recommend eliminating all outliers to ensure that the parameter estimates are more related to the target population, while others encourage retaining, in particular, legitimate outliers [68, 70]. Osborne and his partner [68] have described how a small percentage of outliers can significantly affect even simple analyses, where they have reported that outlier removal enhances the accuracy of estimates for correlations and t-tests, while it greatly reduces errors of inference.

On the other hand, Dhiren and his colleague [70] reported that winsorising by 2.5% would maintain the characteristics of the data and not really change the distribution very substantially. Moreover, they have mentioned that winsorising would alleviate bias by preserving an attenuated version of the outlier rather than eliminating it. In general, outliers may pose critical problems to data analysis. For example, a normal distribution assumption is required for parametric analysis methods and the presence of outliers usually contributes to violate such assumptions, particularly for regression analysis, where outliers can significantly affect the slope, R-value and R Square estimates. Furthermore, outliers can increase the variance of data and therefore minimise the power of statistical tests, which is undesirable.

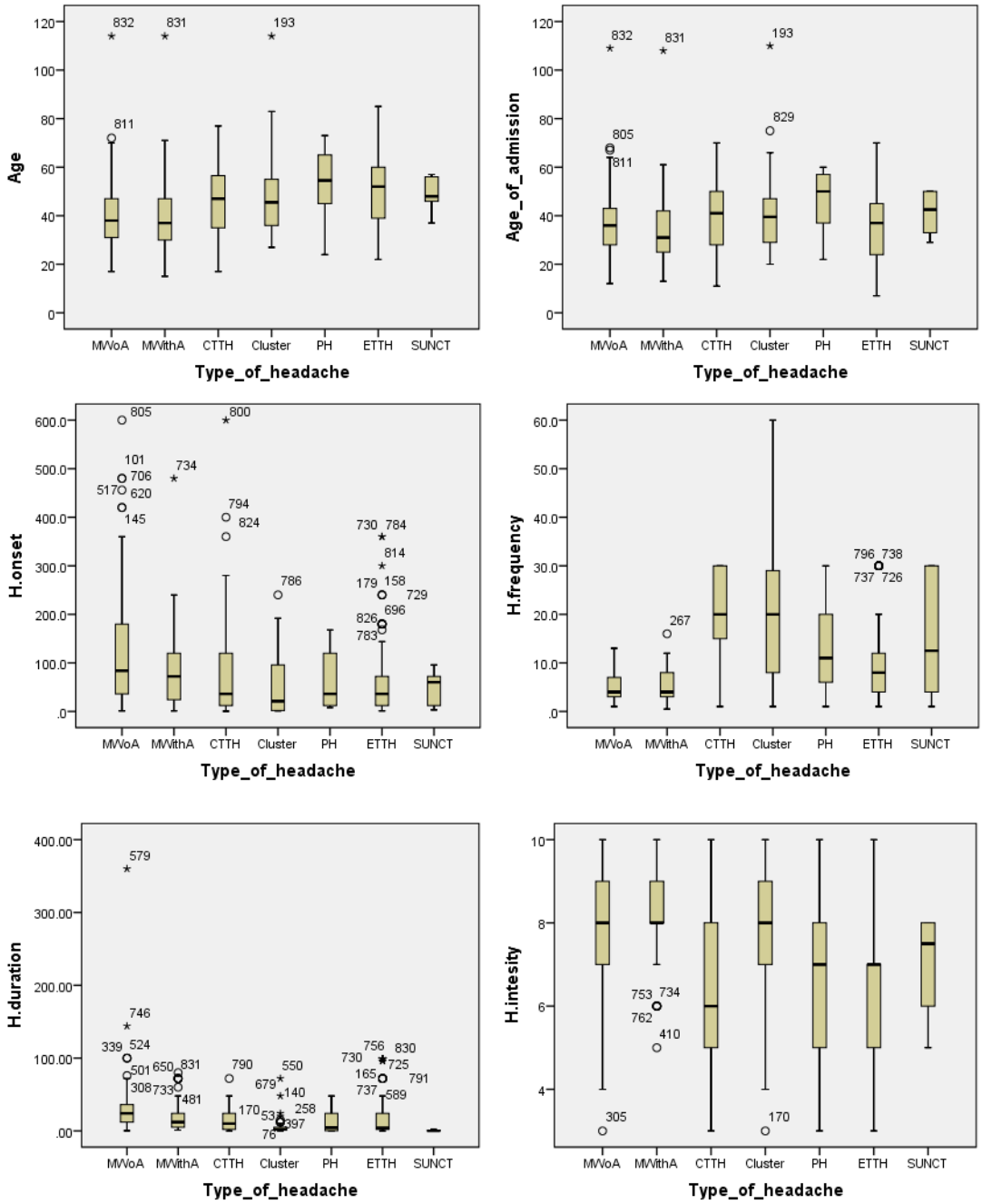


Figure 4-1: Data outliers

Before handling outliers, we need to understand why they exist. As shown in figure 4-1, there are a miniscule number of outliers in the headache data set (0.48% of age, 0.60% of headache frequency, 0.72% of headache intensity and admission age, 2.40% of headache onset and 3.24% of headache duration). Comparing these outliers to the criteria of the International Headache Society (i.e. ICHD-3 beta)[3] revealed that some of them are legitimate extreme observations, which may be inherited from the arbitrary sampling of patients.

For example, the age of onset for migraine patients can range from 15 up to 55 years according to ICHD-3 beta, while the highest observed outlier for migraine patients within the data set was 50 years (record number 805). In contrast, some other outliers exceed the range that was identified by ICHD-3 beta. For instance, the age of onset for patients with tension-type headache may range from 25 to 30 years according to ICHD-3 beta, compared to 50 years age of onset (record number 800), which was the extreme observed outlier for patients with tension-type headache in the data set. Furthermore, let us consider headache duration as another example, where the extreme observed outlier was 360 hours of headache duration for patients with migraine (record number 579), compared to 72 hours as a maximum duration of migraine based on ICHD-3 beta. On the other hand, many other outliers such as record 481 and record 733 fell within the range of duration that was identified by ICHD-3 beta.

Although some outliers represent valid observations, nevertheless, extreme outliers would drastically influence the normality of the data and possibly one extreme outlier can skew the data by a large amount. Therefore, we measured the skewness of the data variables with and without outliers to examine whether outliers could skew our data. In general, the exclusion of extreme outliers seems to decrease variance and degree of skewness remarkably, while maintaining the mean. The skewness of some variables dropped by more than 50%. For example, the skewness of age variable was 0.628, compared to 0.305 without three extreme outliers only. The skewness of headache duration variable decreased from 4.048 to 1.801 when excluding six extreme outliers only. Likewise, the variance of age and headache duration variables reduced by 16.88, 173.47 respectively. Furthermore, the skewness of age of admission variable dropped by 75% from 0.641 to 0.170, and the variance decreased by 41.63 because of excluding three extreme outliers only.

On the other hand, the mean age, age of admission and headache duration variables were very similar. The mean age was 44.98, compared to 44.73 without extreme outliers. Similarly, 37.40 was the mean age of admission, compared to 37.14 when excluding extreme outliers. Finally, the mean headache duration dropped by 0.82%. Thus, it was clear that only a few extreme outliers could significantly influence the distribution of the data as well as raise the degree of skewness dramatically.

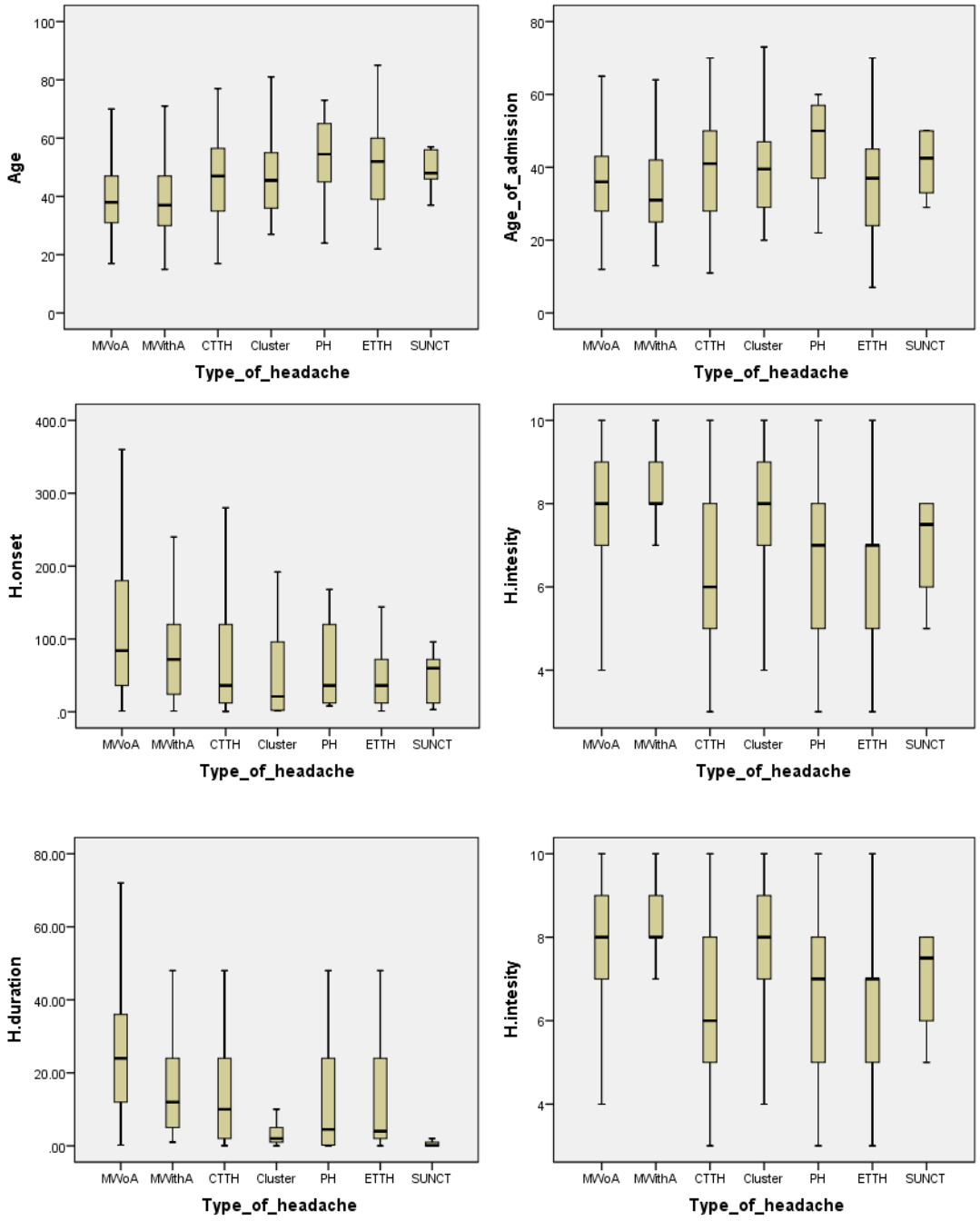


Figure 4-2: Data without outliers

Consequently, we have decided to winsorise the outliers instead of excluding them, as we believe that the presence of outliers in the headache data set is due to the nature of data. Therefore, winsorising outliers, as shown in figure 4-2, would make them closer to the data points through modifying them to the next highest or lowest values that are not presumed to be outlier. As described in [70], winsorising a small number of outliers, i.e. just like our case, would not violate the characteristics of data. However, it would maintain the sample size in particular when the outliers are

legitimate observations. In data pre-processing steps, detecting outliers and addressing them was the first step because they can significantly influence other stages of data processing. For example, the existence of outliers can affect the imputation process, where many other outliers can be produced by imputation.

4.4. Missing Data

Missing data or missing values are very common in real-world data sets, particularly in medical datasets [73]. According to Tran and his colleagues [74], 45% of the data sets in the online data repository UCI have some sorts of missing values. Missing data can occur due to many reasons such as unexpected difficulty in getting some vital measurements. Participants may refuse to answer some questions. The research team may be unable to follow-up all participants during the period of study. Participants' records lack some values due to failure of electronic data storage, and collecting data from heterogeneous sources such as different medical centres, which is the case for our data set. All of these reasons along with many other hidden causes can lead to data losses [75, 76].

Missing data can give rise to serious concerns for classification, where the main concern is the non-applicability of many classification algorithms for such data. Although some algorithms can handle data with missing values by ignoring them, however the majority cannot. Consequently, waste of data and significant classification errors are most likely to occur [77]. Therefore, the first step toward a valid classification process is addressing the issue of "missing data", but we need to consider the nature of the missing data mechanism first, which is a fundamental step to get a valid inference from incomplete data.

4.4.1. Missing data mechanism

A missing data mechanism identifies how the underlying value of missing observation is connected with the reason for being missing [78]. Let us assume Y is NxP matrix containing the data values of P variables (i.e. attributes) for all N units or participants in the sample. Each units denoted by $Y_i = (Y_{i1}, Y_{i2}, \dots, Y_{iP})$. No matter whether the type of response falls under quantitative or qualitative data, Y_j represents the j^{th} measurement for the i^{th} subject or participant at time T_{ij}, where $i = 1, \dots, N$ and $j = 1, \dots, P$, and $Y_{\_j}$ represents all columns in Y_i except Y_j (i.e. the complement

of Y_j). The missing values in Y_i are collectively denoted as Y_i^m, while the observed values in Y_i are collectively denoted by Y_i^o, therefore $Y = (Y^m, Y^o)$ hypothetically represents complete data values. Nevertheless, the values of the part Y^m are unknown for different reasons, and the data accordingly are incomplete [79]. In 1976, Rubin has identified three types of mechanisms under which missing data can occur: First, missing completely at random (MCAR). Second, missing at random (MAR). Third, not missing at random (NMAR) [80].

Data is considered to be missing completely at random (MCAR) when the likelihood that responses are missing is unrelated neither to the observed values, nor to other missing values. In other words, the missing response is independent of both Y_i^o and Y_i^m, which means that the missing values of Y_i merely occurred by chance. Unlike MCAR, data deemed to be missing at random (MAR) when the likelihood that responses are missing depends only on a set of observed values rather than certain missing values. That is, the missing response is merely the result of a chance mechanism that does not depend on the values of another unobserved response. In particular, missing data fall under MAR when the missing response is conditionally independent of Y_i^m, but not Y_i^o. If missing data is not classified as MCAR or MAR, then we are talking about not missing at random (NMAR), which is the third type of missing data mechanism. Missing data is perceived as NMAR when the likelihood that responses are missing depends on both of the following; first, the values that should have been obtained and second, the values that have been actually obtained. To be more precise, missing response is related to Y_i^m and Y_i^o [79, 81].

The significant feature of MCAR is that the observed data Y^o can be perceived as a random sample of the complete data Y. Thus, the observed data inherits the same moments and joint distribution of the corresponding complete data. Consequently, discarding or ignoring missing values Y^m under MCAR would not lead to bias, however it most likely increases the standard error of estimations as a consequence of reduced sample size [79, 81]. Therefore, the observed part of data Y^o can be used to obtain valid estimates of moments, including; mean, variance, and covariance [79].

In contrast to MCAR, the conditional distribution of Y_i^o for subjects with any Y_i^m pattern in MAR would not coincide with the distribution of the corresponding

components of Y_i in the target population. Consequently, the observed data Y^o cannot be thought of as a random sample of the complete data Y. Therefore, calculating mean, variance, and covariance only based on the observed part of data Y^o can lead to biased estimates [79, 82]. MAR and MCAR are showing, in general, the missing response patterns at random and they are usually referred to as ignorable mechanisms, in which the missing values Y^m can be avoided or deleted [73, 81]. Conversely, NMAR mechanism is usually known as a non-ignorable mechanism, in which the missing value Y^m cannot be avoided or deleted because the goal is to make inferences about the distribution of the complete data Y. Therefore, MCAR mechanism seems to pose less threat to statistical inferences in comparison with MAR and MNAR [79, 81].

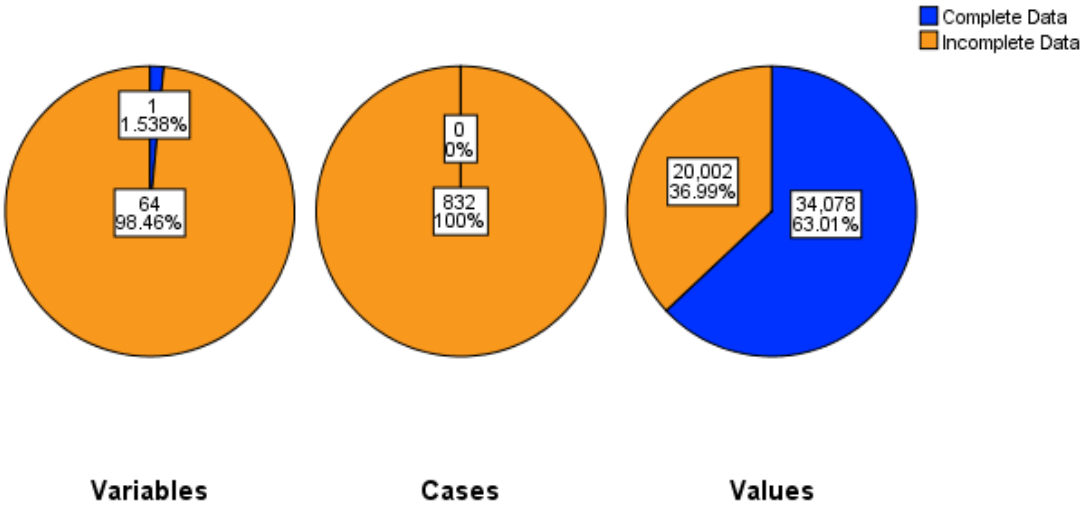


Figure 4-3: Overall summary of missing data

The headache data set as shown in figure 4-3 has 98% of its variables (i.e. attributes) coming with missing values and 100% of cases have some sorts of missingness. Different rates of missingness has been shown, starting from less than one percent for some variables and reaching 100% for some others. Table 4-2 illustrates the missingness rate in descending order. At the bottom of the table, gender and age variables came with missing rates of 1% and 2% of respectively, this seems unrelated to other aspects such as socioeconomic status, disciplinary problems, or any other study-related attributes. However, it is most likely caused by an administrative mistake or a data storage failure.

On the other hand, we have noticed considerably high missing rates in attributes that are related to historical queries, for example asking patients whether they suffered from infantile colic, such responses may not be known for patients themselves, particularly for older patients. This is quite a common type of missing values, where responses are usually "Don't know" or questions are skipped. At the top of the table, some variables are completely missing for example, Fundoscopy explanation variable is 100% missing despite that Fundoscopy variable showed only 13% missing rate. This could be due to the difficulty of interpreting and converting a countless Fundoscopy explanation into numerical or categorical representations. Psychosis is another variable with 100% of missingness. The research team was aiming to collect this variable at the start of their study; however, it might have been left blank because it requires detailed explanation of test results or perhaps due to time limits.

Table 4-2: Variable Summary [a,b]

	Missing		Valid	Mean	Std.
	N	Percent	N		Deviation
Fundoscopy explanation	832	100.0%	0		
PC Psychosis	832	100.0%	0		
Medication overuse duration	818	98.3%	14	3006.64	11128.535
Pain killer using frequency	813	97.7%	19	40.89	60.688
PC Obsession	793	95.3%	39		
MH Infantile colic	758	91.1%	74		
PC anxiety	745	89.5%	87		
Smoking duration	719	86.4%	113	8.075	8.2773
MH OSAS	661	79.4%	171		
MH Snoring	659	79.2%	173		
Medication overuse	642	77.2%	190		
PC normal	625	75.1%	207		
Pericranial muscle tenderness	572	68.8%	260		
PC Depression	554	66.6%	278		
FH Psychopathology	537	64.5%	295		
FH Atopic disorder	537	64.5%	295		
FH Epilepsy	528	63.5%	304		
FH Heart disease	504	60.6%	328		
FH Diabetes	492	59.1%	340		
MH Oral contraceptive	489	58.8%	343		
S Allodynia	486	58.4%	346		
S Osmophobia	479	57.6%	353		
MH Coronary Artery disease	471	56.6%	361		
MH Diabetes	462	55.5%	370		
T Alcohol	461	55.4%	371		
FH Hypertension	455	54.7%	377		
MH Hypertension	428	51.4%	404		
T Skipping meals	425	51.1%	407		

FH Headache	350	42.1%	482		
MH Homocysteinemia	174	20.9%	658		
MH Allergy	161	19.4%	671		
MH TIA/Stroke	151	18.1%	681		
MH Periodic vomiting	147	17.7%	685		
MH Atherosclerosis	144	17.3%	688		
MH Epilepsy	144	17.3%	688		
MH Motion Sickness	143	17.2%	689		
MH Abdominal pain	142	17.1%	690		
MH Surgery	139	16.7%	693		
MH Accident	135	16.2%	697		
MH Hyperlipidaemias	134	16.1%	698		
S Sleep disturbances	115	13.8%	717		
Fundoscopy	112	13.5%	720		
S Vertigo	110	13.2%	722		
T Positional association	106	12.7%	726		
T Seasonal	97	11.7%	735		
Smoking	91	10.9%	741		
S Dizziness	85	10.2%	747		
T Physical activity	84	10.1%	748		
Headache intensity	73	8.8%	759	7.29	1.767
T Menstrual cycle	56	6.7%	776		
Neurological examination	48	5.8%	784		
T Emotional stress	43	5.2%	789		
Headache duration	37	4.4%	795	18.3996	18.86362
Headache onset	34	4.1%	798	79.306	79.9491
Headache frequency	26	3.1%	806	10.161	9.0164
Headache characteristic	23	2.8%	809		
Headache location	22	2.6%	810		
S Vomiting	20	2.4%	812		
S Photophobia	16	1.9%	816		
S Phonophobia	16	1.9%	816		
Age of admission	16	1.9%	816	37.24	12.903
Age	15	1.8%	817	44.83	13.825
S Nausea	8	1.0%	824		
Gender	7	0.8%	825		

a. Maximum number of variables shown: 65

b. Minimum percentage of missing values for variable to be included: 0.0%

Although the above assumptions mostly refer to random mechanisms of missing response (i.e. MCAR or MAR), however further examination is required to identify the specific mechanism that the data belongs to. Accordingly, we have employed the separate-variance t test to help in identifying the variables whose pattern of missingness might be influenced by other quantitative variables [83]. The separate-variance t tests table showed that Osmophobia was most likely to increase the duration of headache, when Osmophobia was missing; the mean headache duration was 17.82, compared to 24.23 when Osmophobia was non-missing. Similarly, the

duration of medication overuse was directly proportional to the duration of headache, when medication overuse was missing, the mean headache duration was 20.40, in comparison to 28.92 when medication overuse was non-missing. The t tests table also revealed that older respondents are less likely to report infantile colic. When infantile colic is missing, the mean age was 45.77, compared to 36.97 when infantile colic was non-missing. Likewise, the missingness of headache duration was influenced by other variables such as Osmophobia and medication overuse.

On the other hand, there were many other variables whose patterns of missingness have not been influenced by other quantitative variables. For example, the duration of medication overuse variable was not influenced by age, the mean age was 44 when the duration of medication overuse was missing and non-missing. Likewise, the frequency of headache does not seem to have been influenced by either, duration of smoking or duration of medication overuse. Overall, the separate-variance t test reveals that data may not be missing completely at random.

To confirm this outcome, we have conducted the Little's MCAR test with an embedded null hypothesis that assumes data are missing completely at random (MCAR). The result of this test appears in the footnote of expectation maximisation (EM) estimate table 4-3. The significant value is less than 0.05 in our test. This matches the conclusion that was derived from the separate-variance t test and can confirm that the data are not missing completely at random. Therefore, the data are most likely to be missing at random. For more details, the complete t tests table is available in appendix A.

Table 4-3: EM Means[a]

Age	Age of Admission	H. onset	H. frequency	H. duration	Smoking duration	P. killer	Med. overuse
44.83	37.24	79.306	10.161	18.3996	12.246	35.305	4306.815
a. Little's MCAR test: Chi-Square = 153.301, DF = 89, Sig. = .000							

4.4.2. Processing of missing data

In general, missing data can be addressed using two different methods, complete case analysis or imputation methods. In the complete case analysis, each Y_i containing Y_i^m is deleted or ignored. Researchers are commonly using this method and it is the

default method in many statistical packages [73]. A survey study revealed that 97% of quantitative studies, that declared the existence of missing values, have used listwise deletion or pairwise deletion to handle missing data [84]. These methods can obtain reliable results when the missing pattern is MCAR [73, 82]. In imputation methods, Y_i^m is filled with imputed values based on other Y_i^o using different statistical measurements. Typically, the quality of statistical inference is inversely related to the proportion of missing values [81].

Up to now, there is no agreed cut-off from the literature showing an acceptable percentage of missing values in a particular dataset for valid statistical inferences. Nevertheless, Schafer [85] has confirmed that a missing rate of 5% or less is insignificant, while Bennett [86] has stated that a missing rate of 10% would possibly lead to biased statistical analysis. Another study by Tabachnick and his colleague [87] showed that missing data mechanisms have more significant impact on statistical inferences than does the proportion of missing data, which makes the proportion of missing values not the main criterion to evaluate the missing data problem [81].

To address the issue of missing data, we are going to hold the stick from the middle. In other words, we are going to discard the variables that meet our threshold of missingness and impute the rest of variables as illustrated in figure 4-4. So let us assume that R is the threshold of missingness, in this study $R = 1/5\,N$, which means that any variable that has a missing rate greater than or equal to R (i.e. 20% of the population N) will be discarded from statistical inferences and from the machine learning stage.

We think that imputing variables with less than the threshold of missingness will not have a serious impact on the quality of statistical inferences and maintains our experiment at the safe side. This is quite different from what some studies have adopted, where generally they are neglecting the attributes that contain relatively low missing rates (e.g., usually less than 15%) and impute the attributes with high missing rates. This course of action might be applicable in certain research areas, but in healthcare applications, it undoubtedly leads to biased statistical inferences or over-fitted machine learning.

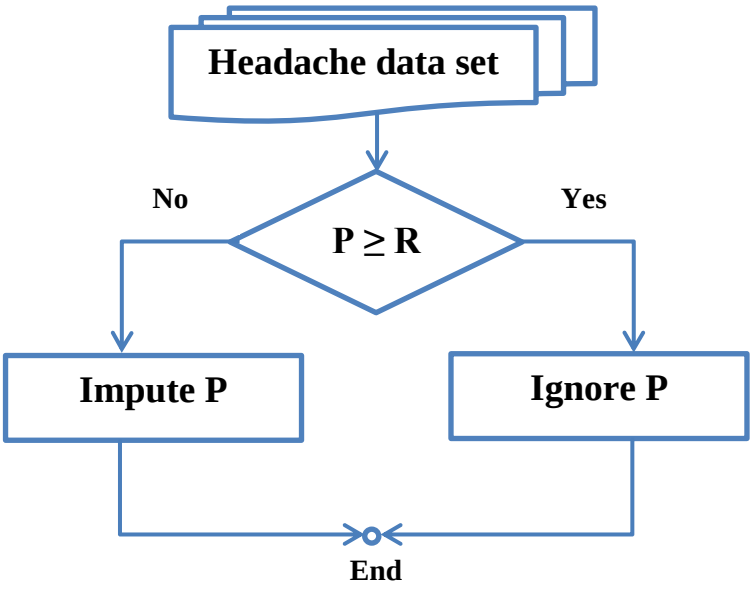


Figure 4-4: Our vision in handling missing data

Although the complete case analysis method (listwise deletion) is the default method of handling missing data in many statistical packages, it is definitely not the appropriate selection for our case study because it eliminates all subjects Y_i that have one or more missing values Y_i^m. Thus, the main disadvantage of the complete case analysis approach is that it is potentially wasteful [82], in particular with our dataset, where 100% of the cases have some sorts of missingness. Moreover, it is not safe to listwise delete cases with missing values as the data is MAR [83]. Therefore, we will discard variables that meet our threshold of missingness rather than listwise delete cases. To state the definition of our method formally, let P be a set of variables (i.e. data columns), where $P = (P_1, P_2, \dots, P_j)$ and j is the dimensions of data set. The observed values in P_i are collectively denoted as P_i^{obs}, while the missing values of P_i are collectively denoted as P_i^{mis}. Hence $N = (P_i^{obs}, P_i^{mis})$. Therefore, the first step in handling missing data would be discarding the variables that meet our threshold of missingness according to equation 1:

$$\forall P_i \in P \leftrightarrow P_i^{mis} \geq R \quad (1)$$

In this context, any data column (i.e. variable) P_i that has missing rate greater than or equal to 20% of the whole population will be discarded. Consequently, 30 out of 65 attributes have been discarded from statistical inference and machine learning as a first stage. Although it is considered 46.1% of the attributes, however we have

maintained 100% of subjects. Stated more precisely, the size of P is reduced to preserve the size of N. Hence, we have a smaller size data matrix $Y = NxP$ with missing rates less than R, but with the same number of patients. Moreover, the majority of discarded attributes are belonging to historical factors, where all family history variables are neglected and less than half of the medical history as well. Indeed, these variables are unrelated to the diagnosis of primary headache disorders as explained by the criteria of IHS [3], which indicates that omitting the outlined variables will not expect to weaken the characteristics of data in particular for applying machine-learning methods.

4.4.3. Multiple imputations

Imputation is the process of replacing missing values with plausible ones, which are derived from observed values. In this study, imputation is the second step toward handling missing values in the remaining variables, where $P_i^{mis} < R$. Let us assume that y is a missing value belong to P_i^{mis} in a particular P_i, carrying out the imputation on a multivariate basis would depend on using the complements of P_i, in other words, using the observed values in the remaining columns P_{-i} as predictors. In contrast, conducting the imputation on a univariate basis would be independent of P_{-i}, but using P_i^{obs} of the corresponding P_i, which means using the observed values from the same column as predictors.

The imputation on a univariate basis (i.e. single imputation) is a very common method to address missing values. There are several imputation methods that impute missing values on a univariate basis. For example, mean imputation is a single imputation method that replaces P_i^{mis} with the average of P_i^{obs} in the same P_i. Mean imputation is a fast and straightforward method to impute missing values; in particular, it maintains the mean of variables when the missing pattern is MCAR. However, many studies have considered that it is most likely to underestimate the variance of the data because it returns a single imputation value for each missing entry in the incomplete variables [76, 82]. In other words, the same value (i.e., mean of observed values) will be used to impute all missing entries.

Last observation carried forward (LOCF) is another single imputation method that replaces P_i^{mis} with the latest observed value in P_i^{obs} of that same subject or

participant. This method is commonly used in longitudinal studies, where participants drop out at some point. LOCF can be valid only when missing values are MCAR; however, it is most likely to produce biased estimates particularly when variables have different level of measurements, such as nominal, ordinal or ratio scales [88]. Therefore, proper accounting of such a variety of scales seems to be inconceivable and potentially leads to impossible values such as negative values [79]. Hot-deck imputation is a very common single imputation method, which replaces P_i^{mis} for a particular participant with P_i^{obs} of a similar participant called donor. Despite its simplicity, the quality of imputed data using the hot-deck imputation method is somewhat similar to the quality of imputed data using nearest neighbour method however, hot-deck imputation method is considerably faster [89].

Although the imputation of missing values on a univariate basis is simple to implement and easy to use, however Myers in [90] has encouraged the research community to avoid using this method when addressing missing data because it involves undesirable concessions in statistical power and may leads to biased estimates. Kombo and his colleagues in [91] stated that there is no guarantee that conducting imputation on a univariate basis leads to a valid analysis even with a strong MCAR assumption. Moreover, it is not safe to impute missing values on a univariate basis when data are missing at random MAR [83]. Therefore, this study is going to adopt imputation on a multivariate basis using a more sophisticated imputation method to address the missing values problem. In fact, advances in computational statistics contribute toward a new wave of flexible as well as formally justifiable imputation methods with a solid statistical basis such as maximum likelihood estimation (MLE) and multiple imputations (MI) [91, 92]. These sophisticated methods are not focusing on replacing missing values only, however they are concerned with getting an accurate estimates of those values as well [90].

Maximum likelihood estimation (MEL) considers the observed values as a representative sample of some distribution, then using an iterative optimisation algorithm, MLE estimates parameters that maximise the likelihood of making the observed values given the parameters [90, 92]. For example, MLE can estimate unknown parameters (e.g. mean and variance) of a normally distributed missing data when some samples of data are observed. Although MEL can be simple and preferable to handle missing values in several scenarios, however with mixtures of

categorical and continuous variables, MLE is not the optimal method as reported by Enders in [92]. In contrast, multiple imputations (MI) offer the flexibility to handle missing values to fit a certain set of analysis objectives and can impute all types of variable including nominal, categorical, ordinal, continuous and binary variables [91, 92]. MI creates multiple imputed datasets, typically two to five, by replacing each of the missing values with a set of plausible values [74, 90-92].

In 1987, MI proposed by Rubin and has become probably the most popular method in addressing missing data due to its convenience, flexibility and considering the uncertainty associated with imputation [74, 91]. In general, MI employs a regression model to fill in missing data on a multivariate basis, where MI treats variables with missing values as outcomes and the rest of variables as predictors. Moreover, it uses Bayesian estimation through iterative algorithm to update the regression parameters with each iteration to avoid using a single set of regression parameters for imputation [92]. After generating m imputed data sets, where $m \geq 2$, the researcher then performs a number of statistical analyses for each imputed data set to obtain imputation-specific parameter estimates. Then these estimates are pooled into a single set of results [88]. Finally, the D imputed data sets are averaged to generate a single complete data set that is used for classification or clustering purposes [74].

In this study, we are going to adopt multiple imputations to handle missing data where $P_i^{mis} < R$. This is mainly because MI is the most sophisticated method that considers the uncertainty associated with the imputation process and it is available in many specialised statistical packages including SAS, SPSS, Stata and the MICE package in R. In addition to the fact that MI supports a mixture of variables, which is what we have in the headache data set that includes continuous, categorical, ordinal and binary variables. Craig has confirmed that MI is generally a more suitable method to address behavioural science missing data because it allows the researchers to customise the imputation procedure to meet the desired goals [92]. Furthermore, it is recommended by the statistical package SPSS that using multiple imputations is safe when data is missing at random [83].

After declaring the pathway for imputation process, we are going to use SPSS statistical software to perform multiple imputations m times, where in this study $m = 5$. This means creating five imputed data sets, which is typically sufficient. The next

step is to define the imputation method, where the fully conditional specification (FCS) method is automatically selected by SPSS as the data showed an arbitrary pattern of missingness rather than a monotone pattern of missingness. FCS is an iterative Markov Chain Monte Carlo (MCMC) method that fits a particular imputation model for each variable with missing values. Then FCS, with each iteration, uses all other variables in the model as predictors to impute missing values for the variable being fit [83]. SPSS uses Linear regression (LINR) to impute continuous variables and Logistic regression (LOGR) to impute categorical variables as shown in imputation models table 4-4.

Table 4-4: Imputation Models

Variables	Models	Effects	Missing	imputed
Gender	LOGR	All variables except gender	6	30
S Nausea	LOGR	All variables except nausea	8	40
Age	LINR	All variables except age	15	75
Age of admission	LINR	All variables except age of admission	16	80
S Phonophobia	LOGR	All variables except phonophobia	16	80
S Photophobia	LOGR	All variables except photophobia	16	80
S Vomiting	LOGR	All variables except vomiting	20	100
H location	LOGR	All variables except headache location	22	110
H characteristic	LOGR	All variables except headache characteristic	23	115
H frequency	LINR	All variables except headache frequency	26	130
H onset	LINR	All variables except headache onset	34	170
H duration	LINR	All variables except headache duration	38	190
T Emotional stress	LOGR	All variables except emotional stress	43	215
Neurological exam.	LOGR	All variables except neurological exam.	48	240
T Menstrual cycle	LOGR	All variables except menstrual cycle	56	280
H intensity	LINR	All variables except headache intensity	73	365
T Physical activity	LOGR	All variables except physical activity	84	420
S Dizziness	LOGR	All variables except dizziness	85	425
Smoking	LOGR	All variables except smoking	91	455
T Seasonal	LOGR	All variables except seasonal	97	485
T Positional association	LOGR	All variables except positional association	106	530
S Vertigo	LOGR	All variables except vertigo	110	550
Fundoscopy	LOGR	All variables except Fundoscopy	112	560
S Sleep disturbances	LOGR	All variables except sleep disturbances	115	575

MH Hyperlipidaemias	LOGR	All variables except hyperlipidaemias	134	670
MH Accident	LOGR	All variables except accident	135	675
MH Surgery	LOGR	All variables except surgery	139	695
MH Abdominal pain	LOGR	All variables except abdominal pain	142	710
MH Motion Sickness	LOGR	All variables except motion Sickness	143	715
MH Epilepsy	LOGR	All variables except epilepsy	144	720
MH Atherosclerosis	LOGR	All variables except atherosclerosis	144	720
MH Periodic vomiting	LOGR	All variables except periodic vomiting	147	735
MH TIA/Stroke	LOGR	All variables except TIA/Stroke	151	755
MH Allergy	LOGR	All variables except allergy	161	805

Let us assume that y is a continuous variable, linear regression uses y as the dependent variable and all other variables as explanatory variables in the regression model. Linear regression uses the complete cases to fit the regression model and impute missing values. The imputation values of the continuous variable y may fall outside the range of observed values, therefore the imputation values can be restricted within a user-specified range. Similarly, let us consider y is a categorical variable with K categories, where $K \geq 2$. Logistic regression uses y as the dependent variable and all other variables as explanatory variables. Then using the complete cases, logistic regression fits the regression model to impute missing values [83].

The imputation process repeats five times, as we specified $m = 5$, to create five imputed data sets and the variations among the imputed data sets represent uncertainty in the imputation process. Once the imputation process is accomplished, the imputed data sets are analysed separately to generate multiple analysis results. These results (i.e. parameters to be estimated such as mean or regression coefficient) are then combined in the pooling approach, where the notation $Q(X, Y)$ denotes a function of X and Y. For m imputed data sets, the estimate Q and the estimated total variance T are calculated as described by Rubin's rules [83, 93].

$$\overline{\mathrm{Q}} = \frac{1}{\mathrm{m}} \sum_{\mathrm{i}=1}^{\mathrm{m}} \widehat{\mathrm{Q}}^{(\mathrm{i})} \tag{2}$$

$$T = \overline{U} + \left(1 + \frac{1}{m}\right) B \tag{3}$$

$$B = \frac{1}{m-1}\sum_{i=1}^{m}(\hat{Q}^{(i)} - \overline{Q})^2 \quad (4)$$

$$\overline{U} = \frac{1}{m}\sum_{i=1}^{m} U^{(i)} \quad (5)$$

Where $\overline{Q}$ is the final combination of estimate Q, and $Q = (Q_1, \dots, Q_k)$, which is the parameter to be estimated with k elementns. $\hat{Q}^{(i)} = (\hat{Q}_1^{(i)}, \dots, \hat{Q}_k^{(i)})$, which is the estimated parameter using i^{th} set of imputed data and $i = 1, \dots, m$. B and U are respectively the between-imputation and the average within-imputation variance calculated by the equations 4 and 5. Finally, $U^{(i)}$ is the estimated covariance matrix of $\hat{Q}^{(i)}$ [83, 93].

The pooling approach combines the analysis results of every individual imputed data set to provide a comprehensive look at estimates. Table 4-5 compares the original and imputed data sets to ascertain whether the range seems acceptable. It shows the statistical estimates of continuous variables that were imputed using linear regression. The pooled estimates are presented at the bottom part of the table, where they are quite similar to the estimates obtained from original data. For example, the pooled mean age is 44.85, compared to 44.83 for the original data. Likewise, the pooled mean age of admission is 37.28 in comparison with 37.24 for the original data. For headache variables, the differences in the means between the pooled and original estimates are 0.53, 0.39 and 0.11 for headache onset, duration and frequency respectively. The lowest change in the mean is for headache intensity variable by 0.01 only. The pooling does not average the standard deviations; however, the original and imputed data sets nearly have the same estimates. For instance, the standard deviation of age in the original data is 13.82, compared to 13.73, 13.72 and 13.75 for the imputed data sets.

Table 4-5: Statistics for MI

Imputation Number			Age	Age of admission	Headache onset	Headache duration	Headache intensity	Headache frequency
Original data	N	Valid	817	816	798	794	759	806
		Missing	15	16	34	38	73	26
	Mean		44.83	37.24	79.306	18.3996	7.29	10.161
	Std. Error of Mean		.484	.452	2.8302	.66944	.064	.3176
	Median		44.00	38.00	48.000	12.0000	7.00	7.000
	Std. Deviation		13.825	12.903	79.9491	18.86362	1.767	9.0164
	Variance		191.137	166.490	6391.862	355.836	3.122	81.295
	Percentiles	25	34.00	28.00	17.000	3.0000	6.00	4.000
		50	44.00	38.00	48.000	12.0000	7.00	7.000
		75	55.00	46.00	120.000	24.0000	8.00	15.000
1	N	Valid	832	832	832	832	832	832
		Missing	0	0	0	0	0	0
	Mean		44.86	37.29	79.461	18.8068	7.30	10.210
	Std. Error of Mean		.476	.444	2.7445	.65901	.061	.3120
	Median		44.00	38.00	55.021	12.0000	7.00	7.921
	Std. Deviation		13.739	12.817	79.1635	19.00888	1.750	9.0008
	Variance		188.767	164.269	6266.859	361.337	3.062	81.014
	Percentiles	25	34.00	28.00	18.000	3.0000	6.00	4.000
		50	44.00	38.00	55.021	12.0000	7.00	7.921
		75	54.00	46.00	120.000	24.0000	8.63	15.000
2	N	Valid	832	832	832	832	832	832
		Missing	0	0	0	0	0	0
	Mean		44.85	37.28	80.236	18.8667	7.29	10.255
	Std. Error of Mean		.476	.445	2.7642	.65458	.061	.3137
	Median		44.00	38.00	58.000	12.0000	7.00	7.891
	Std. Deviation		13.735	12.822	79.7309	18.88105	1.751	9.0498
	Variance		188.640	164.393	6357.009	356.494	3.067	81.900
	Percentiles	25	34.00	28.00	18.000	3.0000	6.00	4.000
		50	44.00	38.00	58.000	12.0000	7.00	7.891
		75	54.75	46.00	120.000	24.0000	8.41	15.000
3	N	Valid	832	832	832	832	832	832
		Missing	0	0	0	0	0	0
	Mean		44.85	37.28	79.548	18.8219	7.30	10.311
	Std. Error of Mean		.476	.444	2.7440	.65371	.060	.3132
	Median		44.00	37.92	57.250	12.0000	7.00	8.000
	Std. Deviation		13.720	12.815	79.1487	18.85594	1.742	9.0335
	Variance		188.229	164.214	6264.521	355.547	3.036	81.604
	Percentiles	25	34.00	28.00	18.000	3.0000	6.00	4.000
		50	44.00	37.92	57.250	12.0000	7.00	8.000
		75	54.00	46.00	120.000	24.0000	8.51	15.000
4	N	Valid	832	832	832	832	832	832
		Missing	0	0	0	0	0	0
	Mean		44.87	37.29	79.755	18.7336	7.31	10.314
	Std. Error of Mean		.477	.445	2.7414	.65210	.061	.3157
	Median		44.00	38.00	60.000	12.0000	7.00	8.000
	Std. Deviation		13.758	12.832	79.0742	18.80949	1.754	9.1068
	Variance		189.293	164.656	6252.730	353.797	3.077	82.933
	Percentiles	25	34.00	28.00	18.000	3.0000	6.00	4.000
		50	44.00	38.00	60.000	12.0000	7.00	8.000
		75	54.06	46.00	120.000	24.0000	8.57	15.000
5	N	Valid	832	832	832	832	832	832
		Missing	0	0	0	0	0	0
	Mean		44.84	37.26	80.195	18.7249	7.31	10.269
	Std. Error of Mean		.476	.444	2.7516	.65146	.061	.3115

	Median		44.00	38.00	60.000	12.0000	7.00	8.000
	Std. Deviation		13.739	12.809	79.3671	18.79084	1.753	8.9853
	Variance		188.764	164.064	6299.131	353.096	3.073	80.736
	Percentiles	25	34.00	28.00	18.000	3.0000	6.00	4.000
		50	44.00	38.00	60.000	12.0000	7.00	8.000
		75	54.00	46.00	120.000	24.0000	8.51	15.000
Pooled	**N**	**Valid**	832	832	832	832	832	832
		Missing	0	0	0	0	0	0
	Mean		44.85	37.28	79.839	18.7908	7.30	10.272
	Std. Error of Mean		.476	.445	2.7773	.65752	.061	.3168
	Fraction Missing Info.		.001	.001	.020	.010	.019	.023
	Relative Increase Variance		.001	.001	.021	.010	.019	.023
	Relative Efficiency		1.000	1.000	.996	.998	.996	.995

Furthermore, a head-to-head comparison using multiple regression analysis is typically an appropriate way to assess the overall accuracy and reliability of imputed data sets. Table 4-6 shows the summary of estimates generated by the regression model for each imputed data set individually. The coefficient of determination (R Squared) is the percentage of variance explained by the model. In other words, R Squared tells us how much of the variance in the dependent variable (Diagnosis) is explained by all other variables (Predictors). R Squared is simply the square of the correlation coefficient R and it ranges from zero to one, where the higher coefficient indicates better goodness of fit for the observations [94]. In our case, .891 is the value of R Squared for the original data. This means that our model explains 89.1 percent of the variance in the diagnosis, which is a significantly good result. If we compare the R Squared of original data to those from the imputed data sets, we can observe that they are very similar, which implies the diminutive changes of variance. Another statistical measure we can use to compare original and imputed data sets is the standard error of estimate, which is the average distance that the observed values fall from the regression line [94]. For original data, the standard error of estimate is .696, which is also quite similar to those from imputed data sets. To summarise the statistical results according to tables 4-5 and 4-6, the multiple imputations process using FCS method reveals significantly acceptable pooled results that are confirmed by multiple regression analysis.

Table 4-6: Model Summary

Imputation Number	Model	R	R^2	Adjusted R^2	Std. Error of the Estimate
Original data	1	.944	.891	.883	.696
1	1	.937	.878	.873	.726
2	1	.937	.879	.874	.725
3	1	.938	.879	.874	.724
4	1	.939	.882	.877	.714
5	1	.938	.879	.874	.723

4.4.4. Dichotomous and categorical variables

In the multiple imputations process, there were 26 variables imputed using logistic regression, two of them are categorical variables (i.e. headache characteristics and headache location) and the rest are dichotomous variables. The dichotomous variables were coded as one for the presence of a certain condition and zero otherwise. In general, multiple imputations maintain the frequencies of these variables. For example, with 0.7% missing values in the gender variable, 22.5% of patients were male and 76.8% were female in the original data, compared to 22.63% male and 77.37% female in the pooled estimate.

It is obvious that multiple imputations preserve male to female ratio, where it was about 1/3.41 in both the original and pooled estimate. Similarly, the presence of nausea in headache has been reported by 40.4% of the patients in the original data, while it was 40.6% in the pooled estimate. In the original data, 68.4% of the patients had denied the presence of vomiting as a headache symptom (considering the 2.4% of missing values), compared to 69.3% for the pooled estimate. Furthermore, 34.1% of the patients in the original data had not experienced phonophobia, compared to 34.4% in the pooled estimate. Overall, all the different statistical tests that were carried out to measure the accuracy and plausibility of multiple imputations have revealed a considerably good result, where the multiple imputed data sets were quite similar to the original one. This was clear through the pooled estimates and confirmed by the regression analysis.

4.5. Data normalisation

Data normalisation is the process of rescaling the quantitative attributes with the intention to eliminate impacts of having different levels of measurement [95]. In other words, data normalisation can be employed to get all the quantitative attributes on the same scale. Normalisation is usually applied before learning and feature selection stages mainly because having disparate scales tends to complicate the comparison of attributes and can influence the algorithm's ability to learn. Let us consider the age of patients ranges from 15 to 85 and the headache intensity is between 1 and 10 on a visual analogue scale. Thus, the values in the age attribute are very large when compared to the values in the headache intensity attribute. Then, in this case attributes may overwhelm each other, which impacts the algorithm's ability to learn and influences the measure of similarity or distance among cases [96].

It has been shown in literature that data normalisation could improve overall performance. As mentioned in [97], normalising the data has a great effect on the training process in particular for neural network, which can be very slow when fed with raw inputs. Another experimental study conducted by Jin and others [98] reported that using normalisation methods in general can remarkably increase the training speed of neural network. Furthermore, the predictive performance of multilayer perceptron neural network was further improved after normalising the data in one of our previous studies [95], where R Squared has improved by 0.15 and root mean square of error was slightly decreased.

Data can be normalised using different rules including arithmetic rules using minimum and maximum values, statistical rules using mean and standard deviation, or using sigmoid normalisation function. In general, all different normalisation techniques transform values of the quantitative attributes to lie within a predefined range such as (0, 1) or (-1, 1). In this study, I am going to normalise the quantitative attributes using min-max normalisation method. This means that the largest value for those attributes will be one and the smallest value will be zero according to the following equation [96-98],

$$x_n = \frac{x - x_{min}}{x_{max} - x_{min}} \tag{6}$$

where x is a certain value to be normalised, x_{min} and x_{max} are the minimum and maximum observed values of a given quantitative attribute P_i, $x, x_{min}, x_{max} \in P_i$ and x_n is the new value of x. Selecting the range of (0, 1) rather than (-1, 1) for data normalisation is essentially to unify the quantitative variables with dichotomous variables. Thus, all data attributes will have a minimum value of zero and maximum of one as shown in table 4-7. The main advantage of using the min-max normalisation method is it maintains exactly all relationships in the data [97].

Table 4-7: Descriptive statistics of quantitative attributes after normalisation

Data attributes	N	Minimum	Maximum	Mean	Std. Deviation
Age	832	.00	1.00	.4263	.19627
Age of admission	832	.00	1.00	.4585	.19407
Headache duration	832	.00	1.00	.2692	.26637
Headache onset	832	.00	1.00	.2099	.22008
Headache intensity	832	.00	1.00	.6156	.25042
Headache frequency	832	.00	1.00	.1642	.15101
Valid N (listwise) 832					

4.6. Chapter summary

Comprehensive processing stages have been carried out in this chapter. We start the chapter by describing the data attributes and identifying their level of measurement. Detecting and processing outliers was the first step of the data processing journey, in which we have employed the winsorising method to modifying outliers to the next highest or lowest values within the distribution. Then, we have handled missing data using multiple imputations to generate five complete data samples that have been analysed and tested. Finally, we ended the journey of data processing by normalising the data using the min-max normalisation method in order to have all data attributes on the same scale.

CHAPTER 5: PREDICTIVE MODELS

5.1. Introduction

The advances in data collection capabilities have led to exponential growth of both data dimensionality and sample size. Nowadays, the data are overwhelmed with a large number of features, particularly within the healthcare sector. In general, machine-learning algorithms attempt to learn patterns in data and discover relations among features (i.e. variables); therefore reducing the number of features in a given data set is a fundamental step in building an accurate predictive model. This chapter starts with introducing three different methods of feature selection and then uses a majority vote to obtain the most representative subset of data features. Each one of the selected features will be analysed to investigate its discriminatory power. This chapter also discusses the imbalance of class distribution and presents the methods to address this issue. In this chapter, a number of predictive models will be created and evaluated using a range of statistical metrics. Finally, the chapter ends with pooling the results and discussing the advantages and disadvantages of each predictive model.

5.2. Feature selection

Feature selection is the process of selecting a relevant smaller subset of features in order to enhance the performance of machine-learning algorithms and to minimise the cost of building a predictive model [99, 100]. It is often the case that different features possess different quantities of information. Thus to maintain high performance of classifiers, the researchers are usually preserving the most relevant features whilst discarding irrelevant, redundant, or noisy ones. The aim of this section is to select a subset of headache features that will in one way or another provide more information or describe the proposed data more than any other combination. Kumar and his partner in their literature review [101] have reported that selecting the correct subset of features would improve classifiers' performance in several ways such as, reducing the size and complexity of problem, improving learning speed, minimising the possibility of over-fitting to irrelevant features, and enhancing generalisation capacity.

Many feature selection methods usually use a feature ranking metric as their primary or secondary mechanism to select features. Ranking algorithms determine the strength of a particular feature in discriminating instances into different classes, and then high ranked features are selected [102]. In the literature, many different approaches are already proposed to handle feature selection. These approaches are broadly divided into two general categories, wrapper approach and filter approach [103, 104]. The wrapper approach uses a classifier's performance as an assessment measure to score feature subsets. Each new subset is used to train a classifier, which is tested using cross validation or holdout method. Measuring the classifier's accuracy and error rate provides a rating score for that subset [104]. As the wrapper approaches train and test a particular classifier for each subset, they are very computationally intensive in particular for high dimensional data, where the size of the search space for n features is $O(2^n)$ [105]. Generally, the wrapper approach provides an ideal performing subset of features; however, it conducts the selection of features subset as a black box, which is the main disadvantage of this approach. On the other hand, the filter approach gives heuristic using pre-processing steps and works independently from the learning algorithm [105]. In contrast to the wrapper approach, the computational cost is much less while selecting the features subset. The filter approach attempts to select an optimal subset of features based on distinctive characteristics, where it assigns some weights to the features based on statistical relations with the class labels [103].

Considering the large number of headache features in our data set, and to ensure the best possible selection of features subset, we adopt a majority vote of three different methods. Our hypothesis is to employ two filter approaches and one wrapper approach, then consider the majority vote to select the best subset of headache features. Information gain (IG) and symmetrical uncertainty (SU) are the two filters, while multilayer perceptron (MLP) neural network is the third method. Although using MLP for feature selection poses a huge computational cost, it considers a combination of features to find a subset with the highest predictive value to boost classification accuracy. Conversely, filters are considering features in isolation from each other. Using statistical analysis, filters evaluate the power of features individually in distinguishing instances into different classes. Therefore, a

combination of filters and wrapper methods would ensure selecting the best performing subset of features.

5.2.1. Information gain (IG)

In the field of machine learning, information gain (IG) is the most widely used feature selection method. The state-of-the-art concept behind using IG is to select an ideal subset of features that explains the most information about the classes [106]. With our proposed data set, IG evaluates the worth of headache features by measuring the information gain with respect to the type of primary headache disorders. IG is an information theoretic criterion and entropy-based evaluation method. Entropy is the negative of information and can be seen as a measure of system's unpredictability [107, 108]. The higher the entropy of the feature, the more information is required to identify the type of headache. Likewise, the lower the entropy of the feature, the less information is required to recognise the type of headache. The information contained in a discrete distribution of feature *X* can be given by,

$$H(X) = -\sum_{i} p(x_i)\, log_2\, p(x_i) \tag{7}$$

The $x_i s$ are the discrete feature values and $p(x_i)$ is its probability [109]. In a given data set *S*, let us consider that *X* is the type of primary headache disorder, and *Y* is a particular headache feature. If the observed values of *X* (i.e. headache type) are classified based on the values of feature *Y*, and the entropy of *X* with regards to the classification that is induced by *Y* is less than the entropy of *X* before classification, then we can conclude that there is a relationship between *X* and *Y* [110]. Then, the information embedded in this joint distribution is provided by,

$$H(X|Y) = -\sum_{j} p(y_j) \sum_{i} p\left(x_i|y_j\right) log_2\, p\left(x_i|y_j\right) \tag{8}$$

where $p(x_i, y_j)$ is the joint probability [109]. Mutual information (MI) offers a good measure of feature worth, where a headache feature is more important when the mutual information *MI(Y, X)* between the type of headache and the feature distributions is greater [109]. Information gain is a similar measure, where IG is the

amount of information that is obtained after removing the uncertainty, and defined in the following equation.

$$IG(X,Y) = H(X) - H(X|Y) \quad (9)$$

The conditional entropy $H(X|Y)$ is calculated between a particular headache feature and the type of headache, where the higher value of mutual information, the larger the IG. This indicates better discriminative power in classifying different types of primary headache and the lower probability error.

With a full list of headache features, IG uses the ranker method to rank headache features by their individual evaluation in a descending order. Features arranged from largest IG to smallest IG. To reduce the feature set, we identified an IG threshold of 0.15, by which headache features with less discriminative power can be discarded. Table 5-1 demonstrates the top-ranked headache features, whose IGs are greater than the predefined threshold. The selected features constitute about one-third of the original feature list, while the remaining two thirds of the features have failed to satisfy the IG threshold. Although, dizziness symptom was the closest headache feature to the selected list, however with an IG of 0.124, it has been discarded. All headache features that belong to the trigger's section have recorded an IG value of less than 0.085, in which physical activity gains the lowest IG. Likewise, features that fall under medical history have revealed negligible IG.

Table 5-1: Top-ranked features using IG

No.	Features	Average merit	Average rank
1	Neurological exam.	0.308 +- 0.006	1.3 +- 0.46
2	Headache frequency	0.305 +- 0.007	1.7 +- 0.46
3	Headache char.	0.271 +- 0.009	3.1 +- 0.3
4	Headache location	0.254 +- 0.01	3.9 +- 0.3
5	S. photophobia	0.233 +- 0.01	5.4 +- 0.49
6	Headache intensity	0.222 +- 0.009	5.6 +- 0.49
7	Headache duration	0.203 +- 0.007	7.3 +- 0.46
8	S. nausea	0.199 +- 0.006	8.2 +- 1.08
9	Fundoscopy test	0.191 +- 0.005	9.1 +- 0.3
10	S. phonophobia	0.187 +- 0.008	9.5 +- 1.02
11	S. vomiting	0.174 +- 0.007	10.9 +- 0.3

5.2.2. Symmetrical Uncertainty (SU)

Symmetrical uncertainty is a filter method that assesses the goodness of features in classifying instances into different classes. Let us consider that *X* is a certain headache feature and *Y* is the type of primary headache (i.e. class attribute). The greater *SU(X, Y)* value (i.e. closest to 1) means that feature *X* has the ability to predict primary headache disorders with high accuracy. Conversely, *SU(X, Y)* equal to zero means that *X* and *Y* are entirely independent [111, 112]. In general, the value of SU is normalised between zero and one. Symmetric uncertainty, equation 10, compensates for the bias of mutual information towards features with large number of values [113] such as headache frequency and duration.

$$SU(X,Y) = 2\,\frac{IG(X,Y)}{H(X) + H(Y)} \tag{10}$$

Information gain was a measure of the dependency between headache features and the type of headache; therefore, we selected symmetrical uncertainty as a measure of correlation between headache features and the type of headache. This method gives weight to the headache features depending on their SU value and compensates for the IG's bias towards features that have more values [111]. Similarly, SU uses the ranker method to rank headache features in descending order according to their SU value. Table 5-2 shows the top-ranked headache features with threshold of 0.15.

Table 5-2: Top-ranked features using SU

No.	Features	Average merit	Average rank
1	Neurological exam.	0.269 +- 0.005	1 +- 0
2	Headache frequency	0.246 +- 0.005	2 +- 0
3	Headache location	0.223 +- 0.008	3 +- 0
4	Headache char.	0.203 +- 0.01	4.4 +- 0.49
5	S. photophobia	0.201 +- 0.009	4.6 +- 0.49
6	S. nausea	0.172 +- 0.006	6.5 +- 0.92
7	S. phonophobia	0.165 +- 0.007	7.3 +- 1.1
8	Fundoscopy test	0.164 +- 0.004	7.5 +- 0.5
9	S. vomiting	0.156 +- 0.006	8.7 +- 0.46

5.2.3. Multilayer perceptron (MLP)

MLP is a feed-forward neural network with input layer, output layer and one or more hidden layers in between. Feed-forward indicates that the data flows in only one direction, i.e. from input to output layer [114]. Layers are consisting of a set of neurons (i.e. perceptrons). Each layer is fully connected to the next one, except output layer. All these connections possess weights, which are randomly assigned at first. Neurons receive inputs from an external source or other neurons. In a typical multilayer perceptron model (figure 5-1), each single neuron performs a weighted sum of its inputs, i.e. the neuron adds up its inputs $(x_1, x_2, \dots, x_i)$, weights $(w_1, w_2, \dots, w_i)$, in addition to the bias b as given by equation 11 [115]. Then, neuron thresholds the result using non-linear activation function, usually with a sigmoid activation function (equation 12). The activation function maps the neuron's output Y to a range between zero and one according to the weighted sum and a certain threshold (equation 13) [116].

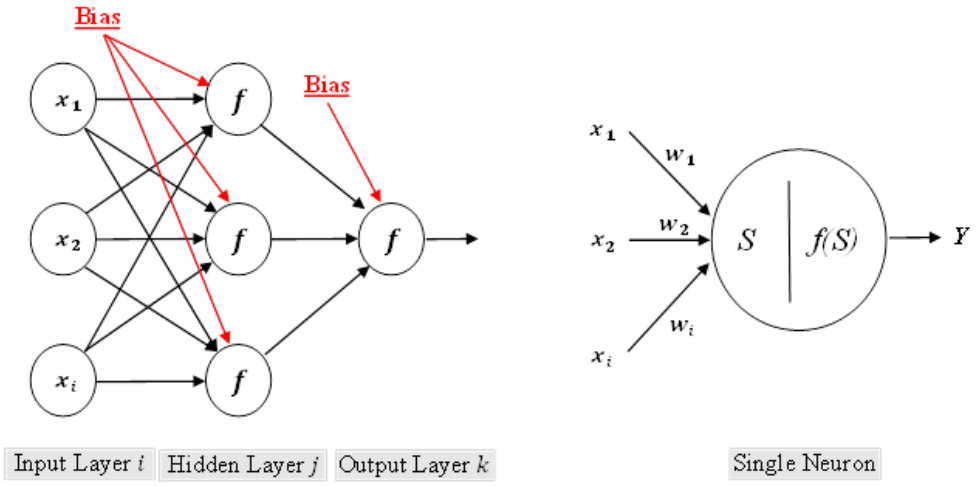


Figure 5-1: A typical MLP neural network

Error at neuron's output is calculated as the difference between desired and predicted output values $\delta = Y_{desired} - Y_{predicted}$. If the predicted output was exactly like or similar to the desired output (i.e. that already known), then, the predictive performance is satisfactory and there is no need to adjust neuron weights. Otherwise, to reduce error at neuron's output, the backpropagation training method adjusts the weights to some extent in an adverse direction to the gradient [117]. Backpropagation adjusts the weights according to the error and learning rate η as shown in equation 14, and then propagates the adjusted weights Δw backwards via

network beginning at output units. This procedure is repeated until the output error is below a predefined threshold [118].

$$S = \sum_i w_i x_i + b \tag{11}$$

$$f(S) = \frac{1}{1 + e^{-x}} \tag{12}$$

$$Y = \begin{cases} 0 & if \sum_i w_i x_i \leq threshold \\ 1 & if \sum_i w_i x_i > threshold \end{cases} \tag{13}$$

$$\Delta w = \eta . \delta_j . x_i \tag{14}$$

MLP has been widely used for an enormous range of supervised classification and regression problems in diverse areas of research. Paliwal and Kumar [119] have presented a comparative review of the use of MLP using 73 various studies that addressed many different application areas. Besides this, MLP is one of the most successful wrapper approaches used for feature selection over the last decade [120, 121]. MLP may start with an empty set of features, all features, or an arbitrary point in the search space. Then using a greedy approach, headache features are sequentially added and/or removed until no single feature can contribute to a better overall performance.

In this study, we use the performance of MLP to evaluate the goodness of the selected subset of features. To be more specific, we use a measure that combines precision and sensitivity (i.e. F-measure) as recommended by Kim and his colleagues [122]. F-measure is a harmonic representation of precision and sensitivity (or also known as recall) that is calculated using confusion matrix [122]. The total number of headache features subsets (i.e. combinations) that were evaluated using MLP was 274 subsets, in which MLP consumes approximately 160 minutes for training and testing using 10 folds cross validation method. With a predefined learning threshold of 0.8, table 5-3 considers a combination of headache features that would ensure output values that exceed the threshold.

Table 5-3: The highest performing feature subset using MLP

No.	Features	Number of folds (%)
1	Neurological exam.	10 (100%)
2	Headache frequency	10 (100%)
3	Headache char.	9 (90%)
4	Headache duration	8 (80%)
5	Headache location	6 (60%)
6	Fundoscopy test	4 (40%)
7	S. dizziness	4 (40%)
8	S. vomiting	3 (30%)
9	MH. epilepsy	3 (30%)

5.2.4. A majority vote

Despite the large computational cost of wrapper based MLP feature selection method, using a combination of feature selection methods is crucial to obtain a precise and reliable prediction. Imagine the learning algorithm has been trained with all features in the data set, it is thought then that all features are good for prediction. However, this conviction is not valid as the data may include irrelevant and/or redundant features [120].

In fact, training learning algorithms with irrelevant features would result in a very poor generalisation performance, increase computational time and over-fitting. Consequently, we adopted a majority vote of three different feature selection methods in order to get an optimal selection of the most representative subset of features that lead to a high performance predictive model. Majority vote is a decision rule that selects headache features, which have more than half of the votes. Accordingly, a certain headache feature will involve creating predictive models, i.e. differentiate between primary headache types, if this feature possesses two out of three votes as demonstrated in table 5-4.

Table 5-4: Features evaluation (all features are considered)

No.	Features	Feature selection methods			
		Filters approach		Wrapper approach	**Majority**
		IG	**SU**	**MLP**	**vote**
1	Headache frequency	√	√	√	√
2	Headache char.	√	√	√	√
3	Headache location	√	√	√	√
4	Headache intensity	√	---	---	---
5	Headache duration	√	---	√	√
6	S. photophobia	√	√	---	√
7	S. phonophobia	√	√	---	√
8	S. nausea	√	√	---	√
9	S. vomiting	√	√	√	√
10	S. dizziness	---	---	√	---
11	MH. epilepsy	---	---	√	---
12	Neurological exam.	√	√	√	√
14	Fundoscopy test	√	√	√	√

5.3. Feature analysis

After considering a majority vote of three different feature selection methods, we need to have a deep understanding of why these features are voted and perceived as relevant features. Technically, the higher the feature ranked, the stronger the relevance of a feature. This means that the top-ranked features are always necessary for an optimal learning performance. On the other hand, features with weak relevance (i.e. that just above the threshold line) may not be always essential for the learning procedure. However, they might become essential for an optimum subset in particular circumstances. In other words, they might be beneficial for the learning procedure when combining them with other strong features. Therefore, an ideal subset should preferably consist of all strongly relevant features and a small subset of weakly relevant features.

It is worthwhile to analyse the final set of features to define their discriminative power in differentiating among various types of primary headache disorders. This step enables us to understand the level of overlap among different types of primary headache. More conveniently separable types of headache that contain reduced overlap among instances from different headache groups, or obvious patterns that

distinguish a certain headache type from another one, will generate much better results during the classification stage.

5.3.1. Continuous features

Starting from continuous features i.e. headache duration and frequency. A simple crosstab analysis shows that 77.46% of patients with trigeminal autonomic cephalalgias TACs (i.e. cluster, paroxysmal hemicrania and SUNCT) are experiencing duration of headache less than 10 hours/day; conversely 74.86% of patients with migraine and 42.29% of patients with tension type headache are experiencing duration of headache more than 10 hours/day. Twenty-four hours duration of headache is approximately reported by 4% of patients with TACs, compared to 29% and 20% of patients with migraine and tension type TTH respectively.

Furthermore, a one-way analysis of variance (ANOVA) can ascertain whether the differences of mean in the headache duration and frequency among patients with different types of primary headache are statistically significant. Figure 5-2 shows an interval plot of headache duration versus the type of headache with 95% confidence intervals (i.e. significance level $\alpha = 0.05$). It is obvious that there are no overlapping areas among the intervals of the three groups, and ANOVA reveals that there is a significant difference in the population means with $p < 0.001$. For this reason, all of the three feature selection methods have considered headache duration feature as being one of the best features with a substantial discrimination capability.

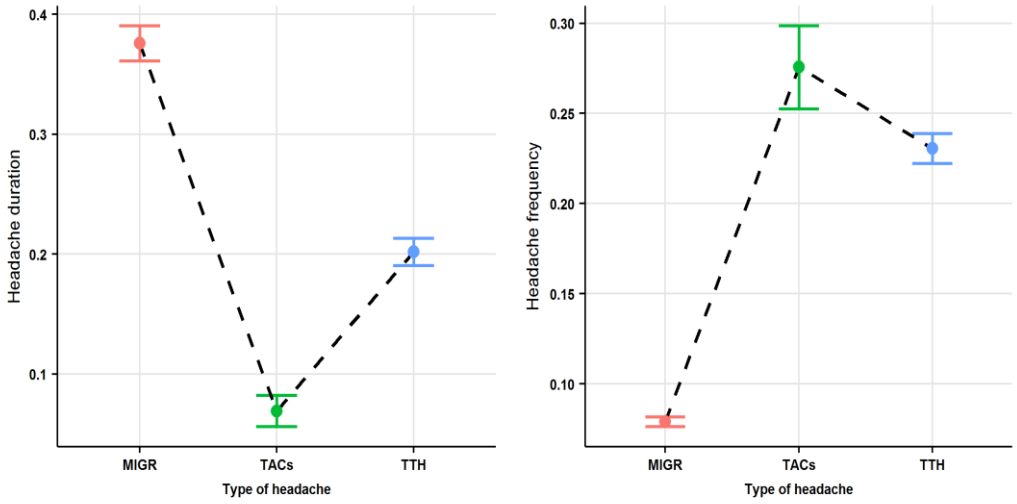


Figure 5-2: Interval plot of level means and confidence intervals of headache duration and frequency

Headache frequency was the second top ranked feature by all of the three feature selection methods; it is measured as the number of headache episodes in one month. Similarly, we use crosstab and ANOVA tests to investigate its capability with respect to differentiating types of primary headache from one another. Crosstab reveals that a large proportion of patients with migraine (i.e. 65.87%) were suffering from five or less headache attacks per month, in comparison to nearly a third of patients with TTH and TACs. Conversely, about half of patients with TACs, none with migraines, and about one third of patients with TTH have recorded high frequencies of headache attacks (i.e. ≥ 20 per one month). The extreme frequency of headache attacks within migraines was 15 episodes/month, which was recorded by one patient. Finally, 2.64% of migraine patients have been subjected to 12 episodes per month. On the other hand, the ANOVA test with 95% confidence intervals shows a significant difference in the population means with $p < 0.001$.

As demonstrated in figure 5-2, the interval level of mean of migraines varies perfectly from TTH and TACs. In contrast to headache duration, the interval level of mean of TTH is relatively close to TACs, but there is no observable overlap between their interval levels of means. It is noticeable that the interval plot of headache duration is almost a pivot rotation of the headache frequency plot. Therefore, combining these two features can conclude that the longer the duration of headache, the fewer attacks occur in a month and vice versa. The discriminatory power of these features lies behind their selection by the three feature selection methods.

5.3.2. Discrete features

The discrete features constitute exactly eighty percent of the selected headache features. Two of them are categorical i.e. headache characteristics and location, while the rest are dichotomous. In this sub-section, we are using cross-tab analysis to examine the discriminative power of discrete features and their relationship with the type of primary headache. Then we conclude with Pearson's Chi-Square test at 95% confidence interval, which is able to ascertain whether there is a significant association between a given discrete feature and the type of primary headache disorders in the sample set.

5.3.2.1 Headache characteristic

Starting from headache characteristics, which is one of the top-ranked features by the three features selection methods. As each type of primary headache has its own specific pain features, patients are usually asked by a specialist to describe the characteristic of the pain that they are exposed to. The characteristic of pain usually falls under one of the following five popular labels; dull, pressing or tightening, throbbing, stabbing, and lightning. Approximately 91% of patients with migraine describe their pain as throbbing, 7% as pressing, 1.5% as stabbing, and 0.5% as dull. Patients with migraine reported no lightning pain feature. Almost 60% of patients with TTH express their pain as dull and pressing, 37.5% as throbbing, 2% as stabbing, while only two patients reported a lightning pain quality. On the other hand, 12.6% of patients with TACs define their pain feature as lightning, 18.3% as stabbing, and 15% as pressing and dull. Finally, 53% of patients with TACs report throbbing pain feature.

Although there is an overlapping area when it comes to how patients precisely describing their pain, however the overwhelming majority of patients are committed to a specific pain label (figure 5-3). For example, throbbing pain was expressed by the vast majority of patients with migraine, half of patients with TACs, and roughly one third of patients with TTH. In contrast, dull and pressing pain was reported by a larger portion of patients with TTH, 15% of patients with TACs, and less than 8% of patients with migraine. Moreover, lightning and stabbing pain was described by one third of patients with TACs, less than 2% for both patients with migraine and TTH. Pearson's Chi-Square test at 95% confidence interval concludes that there is a significant relationship ($p < 0.001$) between headache characteristics and the type of primary headache disorders.

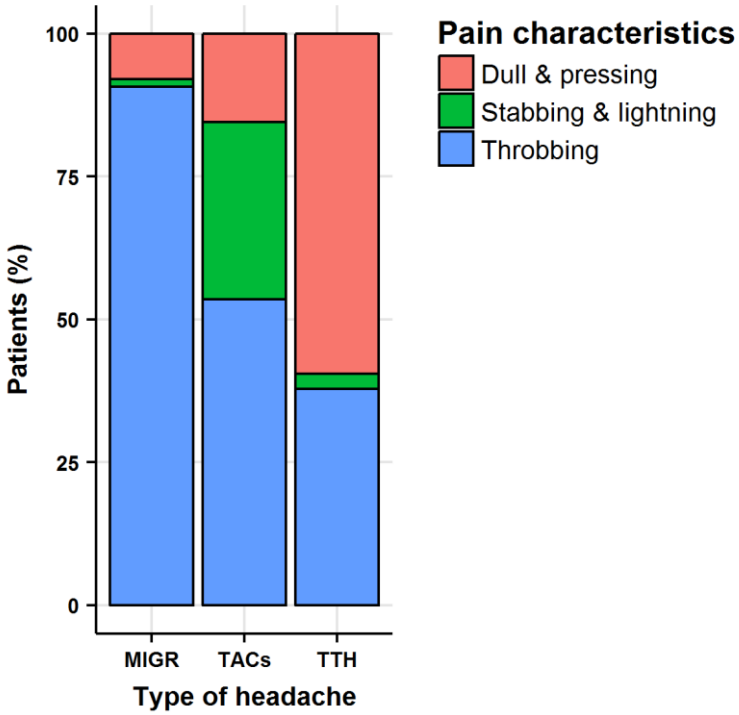


Figure 5-3: How headache patients describe their pain

5.3.2.2 Headache location

Headache location was almost in the middle of the selected features list. Apart from other headache features, the location of pain (i.e. headache) may be on one side of the head (unilateral), on both sides of the head (bilateral), or on other locations of the head as will be explained according to different anatomical positions (figure 5-4). Patients with primary headache have reported five locations of pain, in addition to unilateral and bilateral headache locations. The stated pain locations are frontal pain location that is a yellow coloured area in figure 5-4. Periocular region, which is the area surrounding the eye. Bi-temporal area is the orange coloured on the side of the head in figure 5-4. Occipital location is the green coloured area at the back of the head. Finally, Calvarial or the dome, which is the superior parts of the cranium, including the superior parts of the frontal, parietal, and occipital areas.

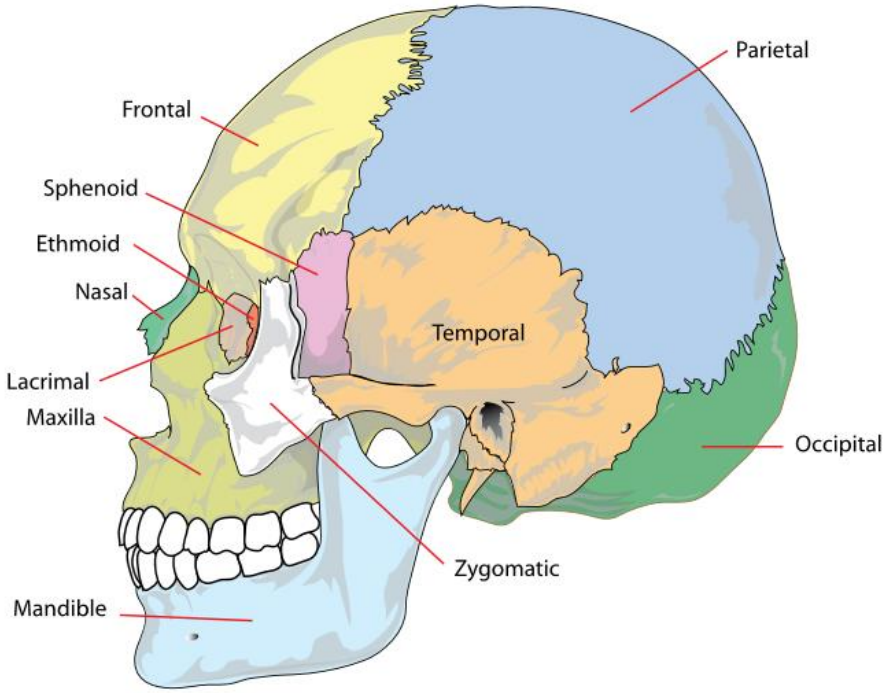


Figure 5-4: Parts of the human skull [3]

A crosstab analysis shows that a unilateral pain location is reported by nearly 65% of patients with migraine and TACs, while barely 7% of patients with TTH. In contrast, about 20% of patients with TTH experienced bilateral and frontal pain locations, which is about double that of patients with migraine who reported the same locations of pain, and seven times as many as patients with TACs. A pain in the area surrounding the eye (i.e. periocular region) was mentioned by almost 20% of patients with TACs, compared to 3.1% and 6.2% of patients with migraine and TTH respectively. Patients with TACs reported no bi-temporal pain location. Conversely, bi-temporal pain location is claimed by about 10.4% of patients with TTH and 7.9% of patients with migraine. Approximately one third of patients with TTH experienced a pain location at the back of the head (occipital), in comparison to 7.1% of patients with migraine and 4.2% of patients with TACs.

For a comprehensive evaluation, we are grouping the recorded pain locations as presented in figure 5-5. The majority of patients with migraine and TACs revealed a one sided headache location, and it was considerably less common among patients with TTH. On the other hand, a pain on both sides of the head was more prevalent among patients with TTH. Moreover, the majority of patients with TTH experienced

a pain location at the front and the back of the head. A pain surrounding the eye area was more widespread among patients with TACs. Lastly, there was no big difference in various types of headache with respect to Calvarial pain location. Despite the fact, that there are slight or near overlaps between different pain locations, which probably was the causative of the current ranking of headache location feature. However, Pearson's Chi-Square test at 95% confidence interval shows that there is a statistically significant association ($p < 0.001$) between the location of headache and the type of headache.

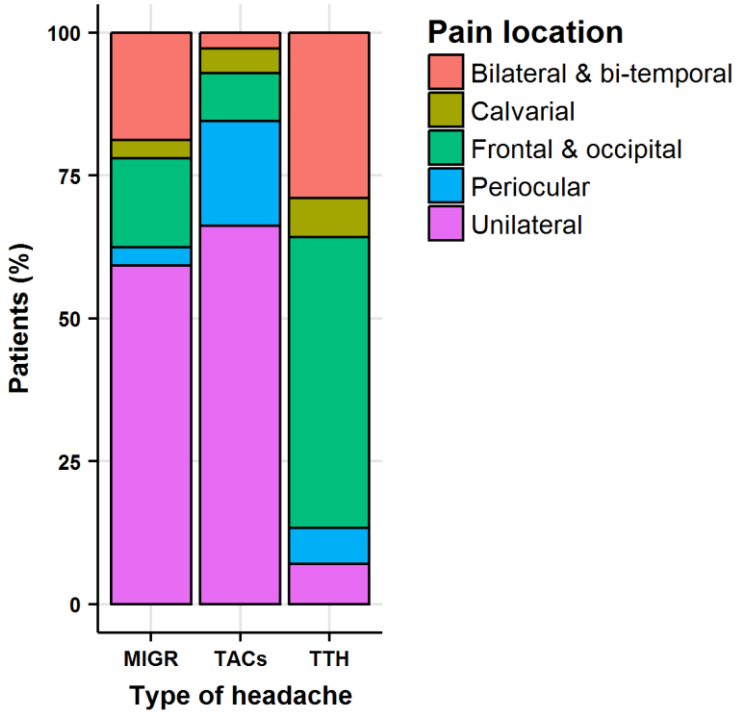


Figure 5-5: Grouping the locations of pain

5.3.2.3 Photophobia and phonophobia

Photophobia is a condition in which patients are unable to tolerate bright lights. In other word, patients are sensitive to any sources of light such as sunlight and bright fluorescent light. Likewise, phonophobia is an abnormal and unjustified sensitivity to sounds that cannot under any conditions be harmful [123]. Patients with phonophobia have a fear of loud sound, as well as regular environmental sounds including traffic noise or loud speech. The sensitivity to light and sound typically accompanies some types of headache and leads to discomfort or even to worsen the pain. A crosstab analysis shows that patients with migraine are most likely to be

sensitive to light and sound during headache. The presence of photophobia and/or phonophobia among patients with migraine was about 90%. On the other hand, approximately two third of patients with TTH and TACs reported no photophobia and/or phonophobia during headache, which indicates that these patients are less sensitive to light and sound. As shown in figure 5-6, the sensitivity to sound, in general, was reported slightly more than sensitivity to light. Photophobia and phonophobia are two symptoms that were selected by only two feature selection methods (i.e. filter methods). However, Pearson's Chi-Square test at 95% confidence interval reveals that they are significantly associated ($p < 0.001$) to the type of headache. Although there is an overlapping area between patient groups, the involvement of these two symptoms along with other strongly relevant features will promote the classification of primary headache disorders.

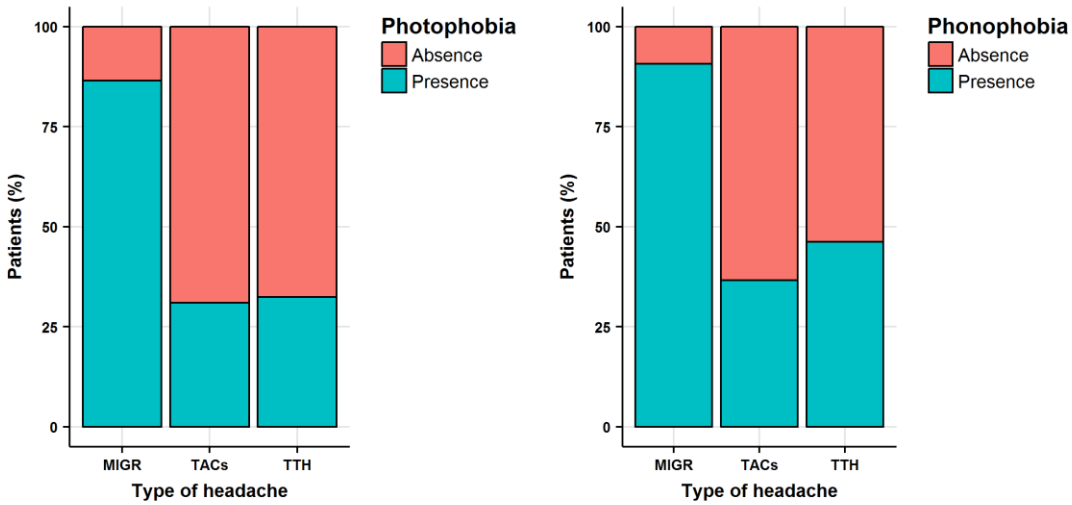


Figure 5-6: The presence of photophobia and phonophobia

5.3.2.4 Nausea and vomiting

Nausea is a kind of discomfort in the stomach, in which patients might feel they need to vomit, however they are not really vomiting. Vomiting is a forced eviction of the contents of the stomach through the mouth, and also known as throwing up [124]. Nausea and vomiting are very common symptoms of headache, particularly in patients with migraine. Nausea was accompanying the headache in 86.77% of patients with migraine, while the presence of vomiting during headache was in about 55% of patients with migraine. As shown in figure 5-7, one third of patients with TTH and TACs have reported nausea during headache, while only 9.66% of TTH

and 15.49% of TACs patients have experienced vomiting during headache. The presence of vomiting was generally less common than nausea for all types of primary headache disorders and particularly in patients with TTH, where less than 10% of those patients have experienced vomiting with headache. All feature selection methods have voted for the vomiting feature to participate in the learning stage, while only filter methods have voted for nausea. Although different types of primary headache may share certain symptoms, however, at 95% confidence interval, Pearson's Chi-Square test confirms that there is a significant relationship ($p < 0.001$) between these two symptoms and the type of primary headache disorders.

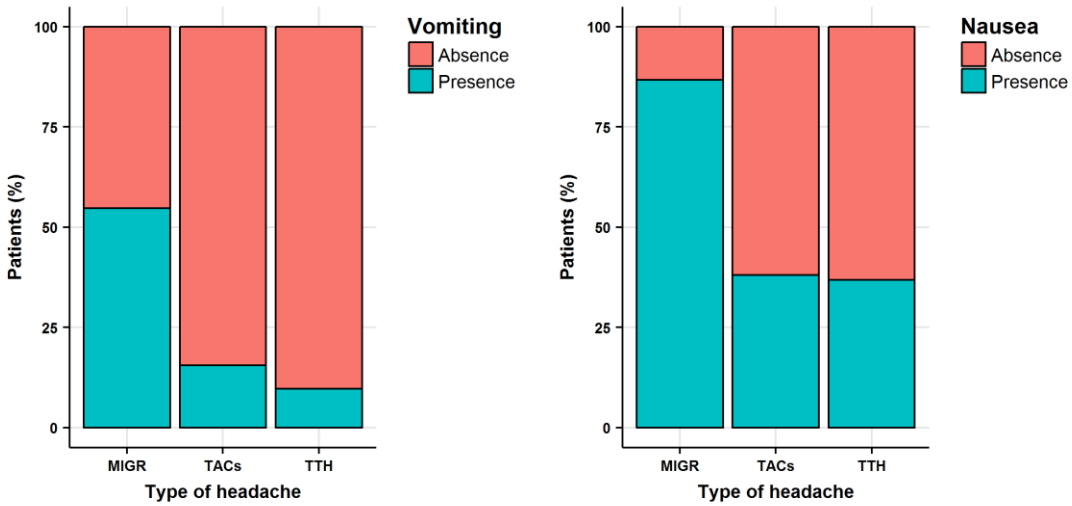


Figure 5-7: The presence of nausea and vomiting

5.3.2.5 Neurological examination and Fundoscopy test

Neurological examination and fundoscopy test are also known as neuro-ophthalmic examination. They are probably the most significant parts of the physical examination in the assessment of patients with headaches. A number of serious and occasionally life-threatening secondary reasons behind headache may possess neuro-ophthalmic signs and symptoms. Comprehending the assessment can also help in making a primary headache diagnosis [125]. A neurological examination is an assessment of the patient's nervous system and motor responses to determine whether the nervous system is impaired. In other words, it is a systematic review of nerve functions in delivering sensory information to the brain and transporting motor orders (peripheral nervous system) and impulses returning to the brain for processing and coordinating (central nervous system) [126].

According to the Scottish intercollegiate guidelines network [4], it is imperative to conduct a neurological examination in particular when patients are presenting with headache for the first time, or when there is a difference in headache pattern. A comprehensive neurological examination should include the following assessments, mental status (e.g. level of alertness, attention, memory, speech and language). Cranial nerves (e.g. fundoscopy test, visual fields, pupillary response, and eye movements). Motor system assessment, in particular muscular contraction, movement at the joints, reflexes and coordination of all limbs. Assessing the sensation of pain, temperature and vibration (i.e. sensory system). Coordination and gait assessment, and finally assessing the neck's mobility and stiffness [4, 126].

Although neurological examination includes a wide range of assessments in addition to the fundoscopy test, however the headache dataset summarise these assessments under two variables (i.e. features). These variables are neurological examination and fundoscopy test. Abnormal neurological examination means that the patient may show an abnormality in one of the mentioned assessments above such as confusion, loss of balance or memory, abnormal reflexes of limbs, blurred or double vision, slurred speech, stiffness of neck muscles.

As shown in figure 5-8, the majority of patients with migraine show a normal neurological examination. An abnormal neurological examination presented in only 5% of patients with migraine, in which about 60% of them were suffering from migraine with aura. Conversely, more than half of patients with TACs and 65.27% of patients with TTH have an abnormal neurological examination. Neurological examination is one of the top ranked features that were voted by all three features selection methods. Moreover, the Pearson's Chi-Square test at 95% confidence interval confirms that there is a significant relationship ($p < 0.001$) between neurological examination and the type of primary headache disorders.

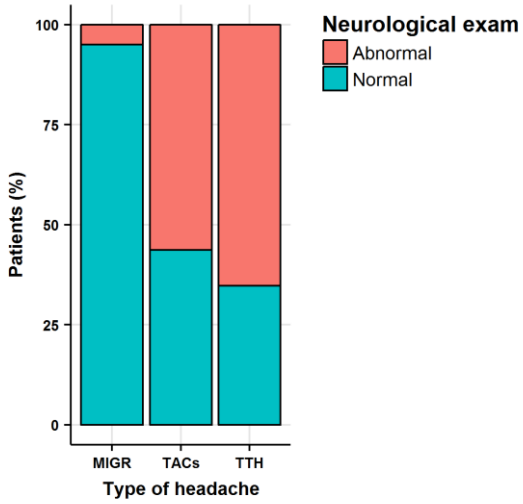


Figure 5-8: Neurological examination result

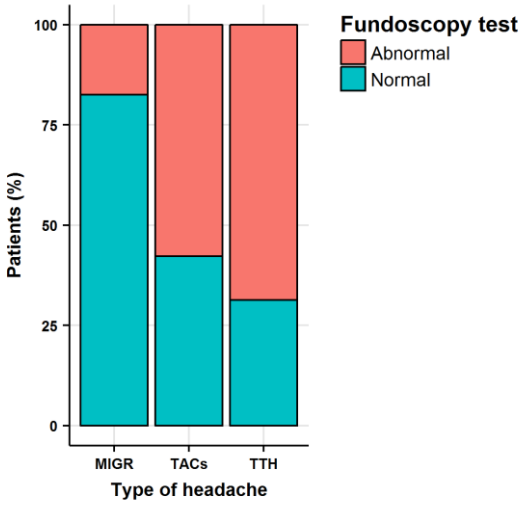


Figure 5-9: Fundoscopy test result

On the other hand, the British Association for the Study of Headache (BASH) [26] stated that fundoscopy test is mandatory for patients who are presenting with headache for the first time, and it is usually worthwhile to repeat it during follow-up. The fundoscopy test allows a visual inspection of the inner eye, also called the retina or the fundus. This visual inspection is clinically valuable as the veins and arteries are visible in their natural state in the inner eye, and many diseases can be detected based on the evidence observed in this location [127]. A crosstab analysis reveals that an abnormal Fundoscopy test was noticed in about two third of patients with TTH, slightly more than a half of patients with TACs, and only in 17.46% of patients with migraine. Moreover, Pearson's Chi-Square test at 95% confidence confirms that

there is a significant correlation ($p < 0.001$) between fundoscopy test and the type of primary headache disorders.

5.3.3. Summary of analysis

The basic insight behind machine learning is to recognise patterns in data and discover ways to identify a certain subject based on the existing variances between subjects. Even though different types of headache can share common features, however they also vary on certain points. Table 5-5 demonstrates the dissimilarities of the final list of headache features in accordance with the type of headache; thus the greater the difference, the more accurate the classification. This section highlights the dissimilarities of headache features within our dataset and harmonises them to many other dedicated headache studies.

As presented in table 5-5, migraine episodes are shown to last longer than TTH and TACs. According to the criteria of IHS [3], migraine attacks last more than four hours and can go up to three days; in contrast to TACs that are characterised by short lasting episodes. The pain in TACs and migraine is unilateral, but it may spread to the entire head during migraine episodes. Leroux and his colleague reported in their differential diagnosis that migraine might attack many patients on alternate sides [126]. Nausea and/or sensitivity to light and sound are the main clinical criteria in differentiating migraine from other primary headaches [3, 4, 26]. These symptoms may occur in patients with TTH and TACs, yet not as much as migraine. It has been shown that nausea, photophobia and phonophobia present in up to 50% of patients with TACs [126], while Turner and others showed that they could overlap with TTH symptoms as well [128].

Haque and his colleagues [129] have spotted that migraine and TTH sufferers share a number of precipitating factors such as anxiety and stress, nevertheless migraine sufferers were significantly sensitive to sunlight. Using self-reported data, Ashina et al. [130] have assessed the one-year prevalence of neck pain in subjects with TTH and migraine. The prevalence of neck pain was considerably higher in patients with TTH. In general, migraine was characterised by a throbbing pain pattern, which presented in roughly half of the TACs patients, conversely, throbbing pain is less prevalent in TTH.

Table 5-5: Selected features evaluation

	Number of patients' n (≈ %)		
	Migraine n=378	Tension-type headache n=383	TACs n=71
Headache duration*			
<5 hours	49 (12.96)	175 (**45.69**)	**49 (69.01)**
5 - 10 hours	46 (12.16)	46 (12.01)	**16 (22.53)**
10.1 - 24 hours	165 (**43.65**)	111 (**28.98**)	5 (7.04)
24.1 - 48 hours	82 (**21.69**)	51 (13.31)	1 (1.40)
>48 hours	36 (9.52)	---	---
Attack frequency*			
< 10 episodes	312(**82.54**)	149(38.90)	21(29.58)
10 to 20 episodes	66(17.46)	153(**39.95**)	**27(38.02)**
> 20 episodes	0(0.0)	81(21.15)	23(32.40)
Headache characteristics*			
Throbbing	343(**90.74**)	145(37.86)	**38(53.52)**
Dull and pressing	30(7.94)	228(**59.53**)	11(15.50)
Stabbing and lightning	5(1.32)	10(2.61)	**22(30.98)**
Headache location*			
Unilateral	224(**59.26**)	27(7.04)	**47(66.20)**
Bilateral or bi-temporal	71(18.78)	111(28.99)	2(2.82)
Frontal and occipital	59(15.60)	195(**50.91**)	6(8.45)
Periocular	12(3.18)	24(6.27)	**13(18.31)**
Calvarial	12(3.18)	26(6.79)	3(4.22)
Headache symptoms*			
Nausea	328(**86.77**)	141(**36.81**)	**27(38.02)**
Vomiting	207(54.76)	37(9.66)	11(15.49)
Photophobia	327(**86.50**)	124(32.37)	22(30.98)
Phonophobia	343(**90.74**)	177(**46.21**)	**26(36.61)**
Neurological examination*	19(5.02)	250(**65.27**)	**40(56.33)**
Fundoscopy test*	66(17.46)	263(**68.66**)	**41(57.74)**

*** p < 0.001**

In contrast to TTH, unilateral pain location presents in two thirds of TACs patients, while about 20% of them reported a periocular pain location (i.e. pain surrounding the eye). Unilateral, periocular, and temporal pain locations are being displayed as a

part of the dominant symptoms of patients with TACs [131, 132]. Although the underlying cause and exact mechanisms of TTH are not known according to the criteria of the IHS [3], however increased tenderness of Pericranial muscles seems to be the most important neurological abnormal finding in patients with TTH. Many recent studies have emphasised the role of muscles in the pathogenesis of TTH and it is becoming gradually obvious that the pain in TTH is of a muscular source [31]. Loder and Rizzoli in their clinical review [30] stated that although muscle tenderness and psychological tension are not evidently the cause of TTH, however they are associated with this type of headache. A controlled study by Anttila et al. [133] shows that increased tenderness of Pericranial muscles is associated with TTH in adults. In another study dating back to 1995, Sakai and his colleagues [134] have measured the hardness of Pericranial muscles (i.e. trapezius and posterior neck regions) of 60 patients with tension type headache and 223 normal healthy subjects. The hardness of trapezius and posterior neck muscles in patients with TTH was significantly greater than that in normal subjects, which led them to conclude that the muscle factor plays a crucial role in the pathophysiological mechanism of TTH. Finally, Lipchik and others [135] have reported that the tenderness of Pericranial muscle was quite effective in differentiating headache patients from healthy subjects, yet failed to identify patients with chronic TTH from those with migraine.

Likewise, many other studies have highlighted the role of myofascial trigger points TrPs in Pericranial muscles and their association with TTH. Myofascial trigger points TrPs are focal disturbances in skeletal muscle, which could direct pain to the head and imitate the pain patterns of TTH [136]. A group of researchers in two different studies have assessed the presence of TrPs in head and neck muscles in patients with episodic and chronic tension-type headache (i.e. ETTH and CTTH) [137, 138]. Active and latent TrPs are present on patients with ETTH and CTTH, while only latent TrPs are present on healthy subjects. In both studies, patients with ETTH and CTTH show greater forward head posture (FHP) and lesser neck mobility. In patients with CTTH, the location of active TrPs played an important role in headache. Longer headache duration was observed when active TrPs were in the right temporalis muscle, while greater headache intensity noticed when active TrPs were in the left temporalis muscle [137]. On the other hand, Doraisamy et al. [139] studied the effect of Myofascial release therapy to the TrPs in patients with CTTH,

where they showed that the therapy has a positive influence in reducing the number of headache days and pain intensity level. Moreover, massage therapy for myofascial TrPs release in patients with recurrent TTH is shown to decrease headache frequency [136].

5.4. Class balancing and Binarization

Primary headache disorders are the most common in the community, with TTH and migraine being the most prevalent. Ahmed in [24] has reported that TTH can affect up to 80% of the population, while migraine has a prevalence of 15%. A multinational European study has also shown that migraine occurs in 15% of the population, whereas TTH in 60%. Cluster headache in particular and TACs in general are very rare with a prevalence rate of 0.3% [140]. Katsarava et al. [141] conducted a community-based survey to estimate the prevalence of cluster headache in the Republic of Georgia. In 1145 interviewed subjects, the prevalence of cluster was 87/100 000. In our patients cohort (n=832), the prevalence of migraine and TTH was 91.5% of the patients population, compared to 8.5% of TACs. The prevalence of migraine and TTH was very close (i.e. migraine was 45.5% and TTH was 46%). According to the IHS classification of headache [3], migraine and TTH are the most common primary headaches, compared to TACs that are very rare in nature. This is what technically known as imbalanced class distribution. It is a very common problem in data mining and machine learning fields.

Imbalanced class distribution is a supervised learning problem where one class enormously outnumbers the other class [142]. This problem is more frequent in binary classification than in multi-class classification, however, it may also occur in one-versus-all schema in multi-class classification [143]. The main complication of the class imbalance issue is evaluating the overall performance of the targeted classifier. Consider training a classifier to classify patients with cluster headache from normal individuals for example, a very big portion of the data, usually 99% describes normal individuals and merely a tiny fraction of the data represents patients with cluster headache. In this scenario, if the classifier always predicts normal individuals, then it is correct in about 99% of the time. However, it is actually worthless in spite of its high accuracy as the minority class (i.e. patients with cluster headache) is the class of interest. Machine learning classifiers can be severely

skewed toward the majority class when learning the class boundary from imbalanced data, which therefore results in a very high false negative rate [143].

On the other hand, imbalance class distribution can occur with Binarization techniques, which is a popular approach in solving multi-class classification problems. Assume that there are N distinct classes; one of the basic multi-class classification techniques built on the top of binary classifiers would be to train N different binary classifiers. Each classifier is trained to differentiate the examples in one class from the examples in all other classes. This process is one-versus-all (OVA) Binarization approach, which builds one classifier for each class. Sen et al. [144] mentioned that the OVA approach might introduce the imbalance class distribution even when it was not existing in the original data. In general, OVA is a straightforward approach that reduces the problem of classifying among N classes into N binary problems. Moreover, it ensures a performance that is more comparable to other complicated approaches, particularly when the binary classifier is adjusted properly [145].

Learning algorithms usually assume that the data has a balance class distribution, but in fact medical data are usually imbalanced as many conditions are quite infrequent, which tend to be the minority class, for example cluster headache [140, 141]. A massively imbalanced data set will therefore have a severe impact on learning and generalisation approach. Sampling methods are widely used to handle this problem, by either dropping some observations from the majority class (i.e. under-sampling) or synthetically adding or even duplicating some observations to the minority class (i.e. over-sampling) [142, 143, 146]. In sampling methods, the data are adjusted in such a manner that produces a more balanced class distribution. This adjustment occurs by altering the size of the data and renders a somewhat similar proportion of different classes. The data then become more adaptable to traditional learning algorithms and we can ensure effective classification accuracy with high confidence.

In the OVA Binarization approach, we have three potential scenarios in building a set of binary classifiers. The class of interest in the first scenario would be TTH, in which the classifier will recognise patients with TTH from other primary headaches (i.e. migraine and TACs). In this case, the data has a balance ratio of 46:54. In the second scenario, the classifier will distinguish patients with migraine from other

primary headaches (i.e. TTH and TACs). This scenario has a very similar balance ratio to the first scenario, which is about 46:54. Finally, TACs will be the class of interest in the third scenario, and the classifier will differentiate patients with TACs from other primary headaches (i.e. migraine and TTH). In typical multi-class classification, Binarization may lead to an imbalance class particularly when K classes have comparable densities. Nevertheless, Binarization worked to benefit our idea in the first two scenarios as we are embedding the minority class (i.e. TACs) once with migraine and another with TTH.

Conversely, there will be a significant class imbalance (ratio 91.5:8.5) when TACs is the class of interest in the third scenario. Therefore, we adopted under-sampling method to ensure that the classifier is capturing the decision boundary between the majority and minority classes. Let us assume that M_j is the majority class for the third scenario (i.e. migraine and TTH), while M_n is the minority class (i.e. TACs). N represents the sample size (i.e. 832 records), and $N = M_j + M_n$. We adopted a random under-sampling method, in which a reasonable subset of M_j was randomly selected and then combined with the minority class sample as a balanced data. In order to achieve a relatively balanced class distribution, the size of new M_j after under-sampling will be approximately 60% of the sample size. This enables M_n to become as much as 40% of the whole data. Therefore, the balanced ratio of the data after under-sampling would be 60:40 in the third scenario.

We have avoided minority oversampling via duplicating TACs records because even if we duplicate 100% of the records, the minority class would not represent more than 15% of the whole sample. As Rahman and Davis have reported in [146], minority over-sampling, despite the longer training time, would potentially lead to an over-fitted learning model. Furthermore, Drummond and Holte in [147] have showed that random under-sampling establishes a reasonable standard for algorithmic comparison, where they examined the interaction of under/over sampling with the C4.5 decision tree classifier using cost curves as performance measure.

5.5. Performance metrics

The overall performance and capability of predictive models can be measured using a range of statistical metrics including sensitivity, specificity and classification

accuracy. These metrics are calculated based on the terms listed in the confusion matrix (table 5-6). Confusion matrix is an unambiguous way to display the prediction outcomes; it plots the true class of interest (i.e. gold standard) in a binary class classification against the predicted class [148]. These terms are represented as true positive (TP), false positive (FP), true negative (TN) and false negative (FN).

Table 5-6: Confusion matrix

	Predicted classes	
	Positives	Negatives
Positives	TP	FN
Negatives	FP	TN

Sensitivity, also called the true positive rate (TPR), is the classifier's ability to identify the class of interest correctly, while the specificity (also called true negative rate TNR) refers to the classifier's ability in excluding the other class correctly. Classification accuracy is the overall correctness of the predictive model, which is the sum of correct predictions (both true positives and true negatives), divided by the total number of predictions made [149]. Classification accuracy is commonly the first step in evaluating the quality of predictive models. However, it could be misleading in some cases especially with a large class imbalance situation [142]. Going back to our cluster headache example, the predictive model achieves high classification accuracy as it usually predicts the value of the majority class, but the model is not useful in the problem domain because it has a very low predictive power. Therefore, sometimes it might be acceptable to choose a predictive model with a lower accuracy just because it provides a greater predictive power on the problem.

Furthermore, we use some other metrics such as precision and F1 score (also known as F1 measure) to provide an objective performance evaluation of their predictive power, in addition to Receiver Operating Curve (ROC) analysis and area under the ROC curve (AUC). Precision or also called positive predictive value (PPV) is the number of true positive predictions divided by the total number of true and false positives [143]. Using precision matrix, we can see how a particular case that been predicted as positive is in fact a positive, as reported by Hoens and Chawla [142].

Accordingly, low precision can reveal that there is a multitude of false positives, thus we can perceive precision as a measure of a classifier's perfectness. Moreover, we can derive a harmonic mean of precision and sensitivity using F1 score as shown in table 5-7, which also called F-score or F-measure.

Table 5-7: Performance metrics

Metrics	Abbreviation	Computation	Scope
Sensitivity	TPR	TP/(TP+FN)	[0,1]
Specificity	TNR	TN/(TN+FP)	[0,1]
Accuracy	ACC	(TP+TN)/(TP+TN+FP+FN)	[0,1]
Precision	PPV	TP/(TP+FP)	[0,1]
F1 score	F1	2*(PPV*TPR)/(PPV+TPR)	[0,1]

On the other hand, ROC analysis is a standard technique that is designed to summarise the predictive performance of binary classification models. The ROC curve plots the true positive rate (TPR) against the false positive rate (FPR) measurements at diverse decision thresholds in two-dimensional ROC space [142].

An ideal predictive model would have a point in the upper North West corner of the ROC space, which means that the model has accurately classified all the positive and negative classes. In contrast, a model with random prediction performance will fall along the diagonal line of the ROC curve, in which TPR and FPR are equal over all different decision thresholds. The ROC curve analysis is widely accepted in the medical field, where it provides perfect details of the model's predictive performance particularly with imbalanced data. From this graphical representation, we can select an optimal decision boundary, as well as consider the AUC metric.

5.6. Predictive models

The diagnosis of headache relies entirely on the history and examination. A history plays an important role in the assessment of headache, where headache symptoms and characteristics should be described as completely as possible. According to the Scottish intercollegiate guidelines network [4], healthcare professionals commonly find it difficult to diagnose headaches, and headache sufferers are usually concerned about serious rare causes of headaches such as brain tumours. Here comes the role of examination to exclude secondary causes of headache, or to differentiate chronic

TTH from migraine as an example. In the UK, General practitioners refer about 3% of patients with headaches to specialist neurology clinics as a way to exclude secondary causes of headache, or for a more accurate diagnosis [150]. The majority of primary headaches can be managed in primary care and specialist's assessment is occasionally required.

The aim of the present study is to assess the capability of machine learning (ML) methods in the diagnosis of primary headaches. The involved ML methods are decision tree (RPART), adaptive boosting model (ADA), random forest (RF), support vector machine (SVM), logistic regression (LOGR) and artificial neural network (MLP). In this research, we measure the sensitivity, specificity and classification accuracy of six popular supervised ML algorithms using clinical data.

The data set consists of patients' records with the main types of primary headaches including migraine, TTH and TACs. The data set went through a comprehensive processing stage to ensure effective and reliable results. Using the holdout method, we divided the dataset into 60:40 ratios for training and testing respectively. This section presents the evaluation of six predictive models in a binary approach (i.e. OVA approach) and results are then pooled. We conducted the experiment using R statistical computing language, and evaluated MLs on a PC computer with 3.40 GHz Intel Core i7 CPU, 16 GB main memory and running Windows 7 Enterprise 64-bit operating system.

5.6.1. Tension type headache vs. all

The evaluation results of the predictive models in diagnosing TTH are presented as follows. Table 5-8 lists the results from the experimental procedure for each model in terms of the six performance metrics considered, in addition to the overall error and required training time. Figure 5-10 demonstrates the AUC values resulting from ROC analysis, along with F1 measure as a harmonic indication of precision and sensitivity. Figure 5-10 provides a visual assessment for the overall performance of classifiers' responses in classifying TTH from other primary headaches.

Table 5-8: TTH vs. All results using holdout method

Predictive Model	TPR	TNR	PPV	F1	ACC	AUC	Overall error (%)	Time (Seconds)
RPART	0.884	0.588	0.766	0.821	0.767	0.807	23	0.01
ADA	0.865	0.735	0.833	0.849	0.813	0.873	19	0.37
RF	0.884	0.735	0.836	0.859	0.825	0.891	17	0.09
SVM	0.884	0.705	0.821	0.851	0.813	0.880	19	0.03
LOGR	0.865	0.676	0.803	0.833	0.790	0.811	21	0.02
MLP	0.942	0.617	0.790	0.859	0.813	0.800	19	0.03

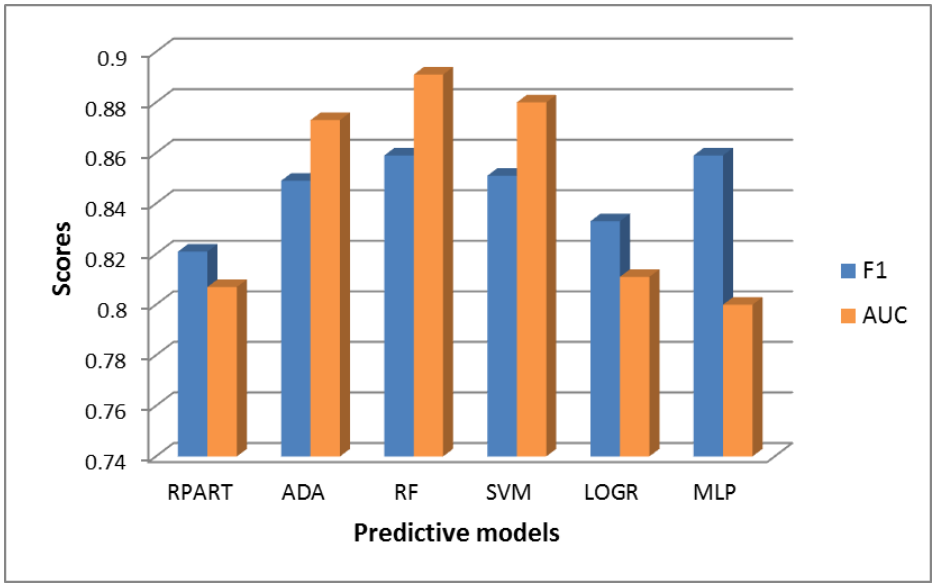


Figure 5-10: Performance of MLs (TTH vs. All)

It can be spotted that almost all of the models systematically yield AUC values of greater than 0.8, where RF model achieved highest AUC value of 0.89, lowest overall error and reasonable training time. MLP was the most sensitive model to distinguish TTH from other primary headaches. RPART, RF and SVM reached a sensitivity of 0.884, followed by LOG and ADA with a sensitivity of 0.865. Although RF and MLP reached F1 measure of 0.859, however, RF was superior with both AUC and classification accuracy. Both ADA and AVM models showed classification accuracy of 0.813 and an overall error of 19%, but SVM showed a better sensitivity, while ADA revealed a superior specificity. All models produced considerably better sensitivities than specificities with respect to diagnosing TTH from other primary headaches.

5.6.2. Migraine vs. all

This sub section presents the evaluation results of the classifiers with respect to the diagnosis of migraine. Table 5-9 illustrates performance metrics using holdout method. It is obvious that all of the predictive models have reached much higher specificities than sensitivities. RPART and MLP models have yielded identical results with exception of the AUC and training time, and they yielded the highest sensitivities among other learners. Likewise, ADA and SVM have also showed precisely the same evaluation results with exception of AUC and training time, where ADA was the most time consuming classifier. RPART and MLP models have achieved an AUC of 0.899 and 0.896 respectively, while the rest of the models have reached AUC value greater than 0.95. As shown in table 5-9, F1 measures were very much the same for the classifiers, with very little variation. The highest possible value of classification accuracy was 0.903 and reached by ADA, RF and SVM models.

Table 5-9: MIGR vs. All results using holdout method

Predictive Model	TPR	TNR	PPV	F1	ACC	AUC	Overall error (%)	Time (Seconds)
RPART	0.809	0.944	0.894	0.85	0.894	0.899	11	0.01
ADA	0.785	0.972	0.942	0.857	0.903	0.962	10	0.39
RF	0.761	0.986	0.969	0.853	0.903	0.959	10	0.10
SVM	0.785	0.972	0.942	0.857	0.903	0.954	10	0.04
LOGR	0.785	0.944	0.891	0.835	0.886	0.961	11	0.03
MLP	0.809	0.944	0.894	0.85	0.894	0.896	11	0.03

5.6.3. TACs vs. all

Table 5-10 shows the performance measure of the predictive models with respect to diagnosing TACs. It can be observed that almost all of the classifiers yield AUC values greater than 0.85, with the exception of evaluation over the MLP and RPART models that show a slightly lower values. The highest sensitivities were achieved by MLP model, followed by ADA model and then LOGR model, where these models have achieved diagnostic sensitivity greater than 0.9. The classifiers consistently yield F1 and overall error values. The highest classification accuracy outcome over the TACs class was obtained by ADA model, yielding a value of 0.813. MLP model has reached the second highest classification accuracy with 0.8, followed by RF and

LOGR models that yield an accuracy value of 0.791. As presented in table 5-10, AUC values for nearly all of the models were higher than their F1 values, with exception of MLP model that achieve highest F1 value. Finally, both of RF and SVM show greater specificities than sensitivities in contrast to all other models.

Table 5-10: TACs vs. All results using holdout method

Predictive Model	TPR	TNR	PPV	F1	ACC	AUC	Overall error (%)	Time (Seconds)
RPART	0.88	0.658	0.758	0.814	0.78	0.836	22	0.01
ADA	0.94	0.658	0.77	0.846	0.813	0.908	19	0.4
RF	0.738	0.923	0.96	0.834	0.791	0.918	21	0.21
SVM	0.727	0.92	0.96	0.827	0.78	0.857	22	0.03
LOGR	0.92	0.634	0.754	0.828	0.791	0.853	21	0.04
MLP	0.94	0.625	0.758	0.839	0.8	0.807	20	0.03

5.7. Pooling and discussion

This section pools the evaluation results of the predictive models (i.e. classifiers), but before starting let us highlight some of the general observations from performance evaluation sections. Starting from TTH versus others, all of the classifiers have registered considerably higher diagnostic sensitivities than specificities. In contrast, specificities were noticeably larger than sensitivities for all of the classifiers when diagnosing migraine from others. Unlike previous models (i.e. TTH and migraine), there was a performance fluctuation with respect to the diagnosis of TACs, where some of the classifiers reached higher sensitivities, while others achieved better specificities.

There was a fair balance between F1 and AUC values for all of the predictive models with respect to diagnosing migraine; moreover, the classification accuracy of migraine was much higher than TTH and TACs. Conversely, there was a lack in such a harmony between the values of F1 and AUC in the diagnostic performance of both TTH and TACs. Very similar classification accuracy was observed with respect to the diagnosis of TTH and TACs. The classifiers expressed relatively larger overall error rates with the diagnosis of TACs, followed by TTH and then migraine.

On the other hand, figure 5-11 shows the trade-off between true positive rate (i.e. sensitivity) and false positive rate (i.e. 1-specificity or type 1 error α) across a series

of decision boundaries plotted in the ROC space. It is another effective analysis method to evaluate the overall performance of the classifiers. On observation of the ROC plots, all models tend to exhibit greater capabilities in the diagnosis of migraine than other primary headaches, where all the curves of migraine versus all are close to the upper left corner of the ROC space.

It is also clear on the ROC space that nearly all of the classifiers have yielded slightly better results in the diagnosis of TACs than TTH, with the exception of the SVM learner. The similarity in the performance profile between PRART and MLP models, with a few exceptions, can be confirmed in terms of migraine diagnosis. Moreover, all other models appear to exhibit a similar behaviour over the migraine diagnosis as well. RF and ADA models stand out in the ROC space with respect to TACs; they are also, in addition to SVM, showing a very similar performance profile when diagnosing TTH and migraine.

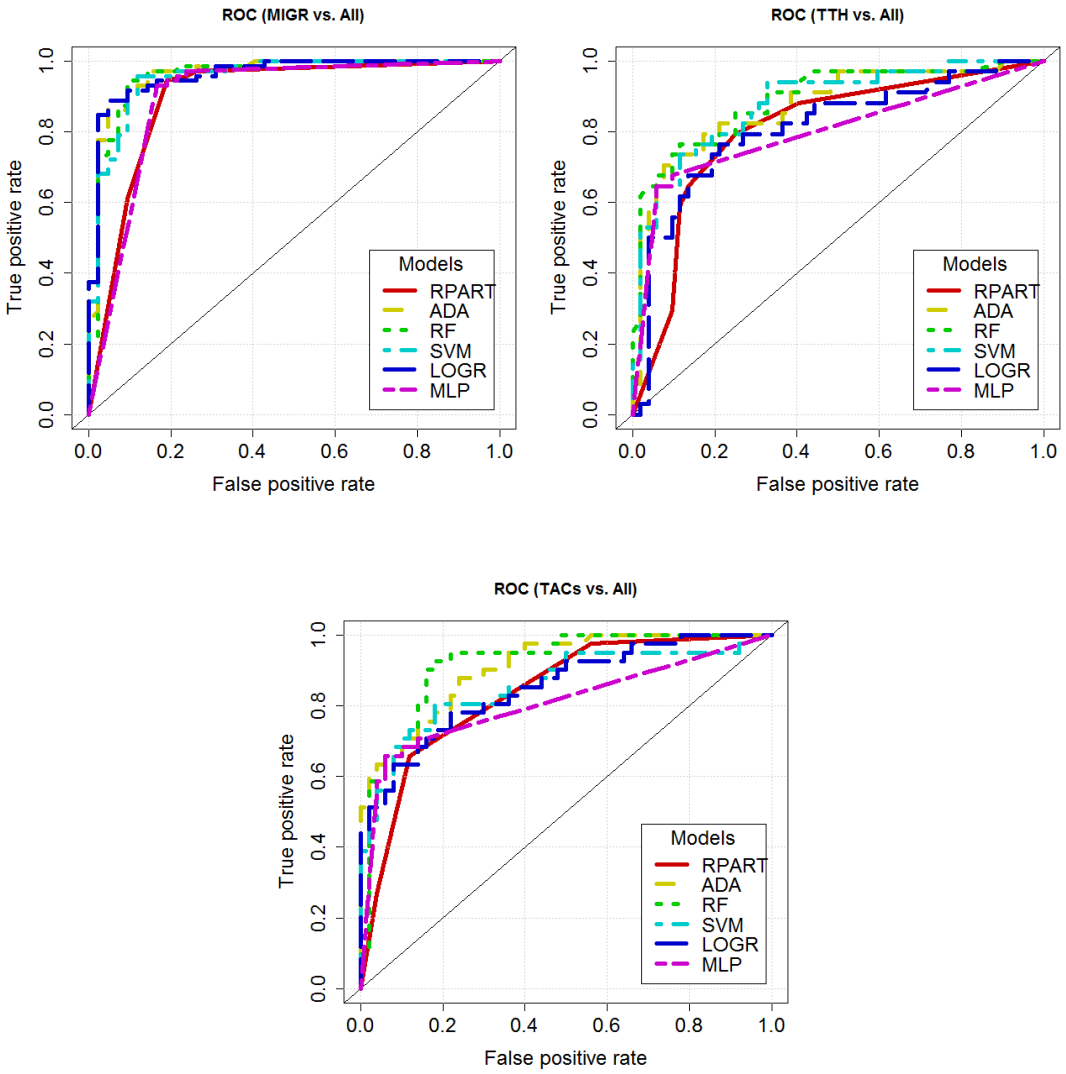


Figure 5-11: ROC Plots for the models

The initial scene that we can come through using OVA approach and ROC analysis, with respect to different types of headache, is that migraine was the most well classified headache, followed by TTH and then TACs. We can consider such a context, regardless of some tiny variations, as a generic insight that covers all of the targeted classifiers in this study. This is most likely to be due to the distinctive characteristics of migraine, where all of the migraine's related features (i.e. nausea and/or sensitivity to light and sound) have been involved with the final set of the data as specified by features selection methods.

In addition to the ROC analysis, the pooled results in general can provide a comprehensive view of the model's diagnostic power. Since we have guaranteed a particularly reliable and balanced class distribution and obtained performance

evaluation results over OVA approach, we compared the overall diagnostic power of the predictive models using the pooled results from table 5-11, after calculating performance metrics for each type of headache individually. Pooling results is the main step toward classifiers' assessment. It reveals the overall capacities of the classifiers in diagnosing all of the three types of primary headache. From the pooled result, we have built a comparison that is primarily based on precision and recall (i.e. TPR and PPV), in addition to the F1 measure, which is their single combined representative. We also took into consideration the pooled accuracy and area under the ROC curve. The use of precision and recall are very common in the assessment of predictive models as they represent or express both type 1 and type 2 errors (α and β respectively).

Table 5-11: Pooled results

Predictive Model	TPR	PPV	F1	ACC	AUC
RPART	0.858	0.806	0.828	0.814	0.847
ADA	0.863	0.848	0.851	0.843	0.914
RF	0.794	0.922	0.849	0.84	0.923
SVM	0.799	0.908	0.845	0.832	0.897
LOGR	0.857	0.816	0.832	0.822	0.875
MLP	0.897	0.814	0.849	0.836	0.834

Predominantly, all of the predictive models have achieved considerably good results, however the highest sensitivity (i.e. TPR or recall) was about to reach 0.9 and achieved by MLP model, followed by ADA model with a sensitivity value of 0.86, then PRART and LOGR that showed somewhat similar sensitivities. Eventually, SVM and RF models have achieved a sensitivity value of slightly less than 0.8. Sensitivity refers to the classifier's capability to correctly identify certain types of headache from others. To be more precise, for all cases that actually diagnosed a migraine for example, sensitivity measure shows how many of these cases were accurately captured by predictive models. In this context, the probability of making type 2 error, i.e. called false negative rate FNR, which in this case is falsely classifying the type of headache, is inversely proportional to the sensitivity as shown here $\beta = 1 - TPR$. This means that higher sensitivity can ensure lower β, which in turn contributes to a better predictive model.

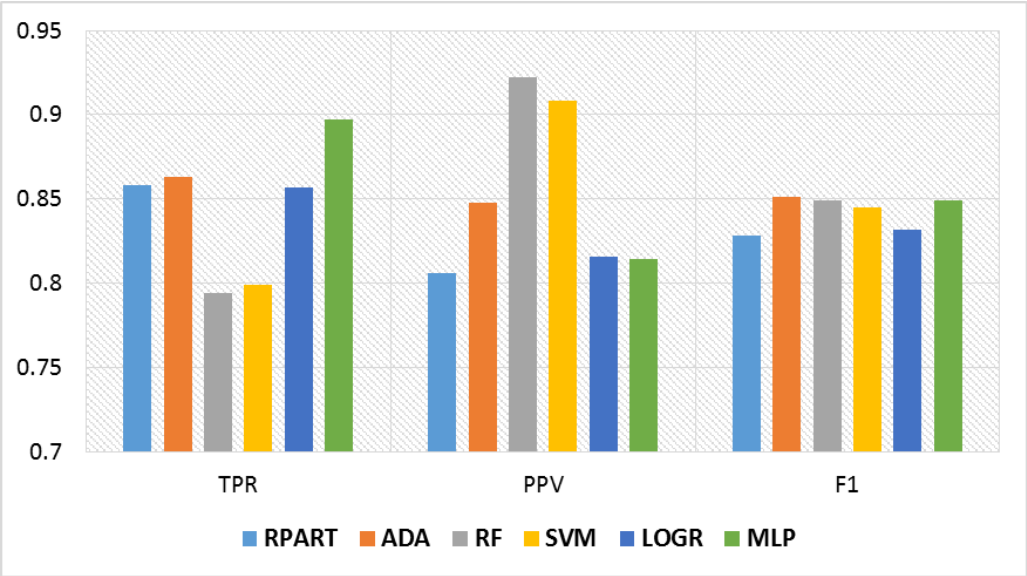


Figure 5-12: Pooled TPR, PPV and F1 measures

In contrast to the sensitivity measure, it can be noticed from figure 5-13 that almost all of the models have shown an inverse behaviour with respect to the precision measure, i.e. PPV. Models with low sensitivity have produced the highest precision and vice versa. RF model has achieved the highest precision value of 0.92, followed by SVM and ADA models respectively. MLP, LOGR and RPART models have gained very similar precision values. Precision is indicative of the model's accuracy on condition that a particular type of headache has been predicted. In other words, how realistic is the model when it claims that a certain case is positive? Consequently, low precision can expose that there is a large number of false positives, i.e. false alarms, and hence an elevated type one error.

Although there is a clear variation between sensitivity and precision measures as presented in figure 5-12, nevertheless F1 scores are very much the same for virtually all of the models. This is mainly because F1 measure provides a general idea of the model's predictive capabilities, no matter what type of error has occurred. In the real world, type 1 and type 2 errors cannot be entirely prevented; however, it has been recommended that increasing the sample size would reduce the likelihood of their occurrence. This might be one of the reasons that led to high error rate with respect to the diagnosis of TACs in the third scenario, where we have tried to create a balance distribution of class labels, which in turn affects sample size in one way or another. Moreover, as presented in table 5-5, TACs share few features with migraine

and TTH. It can be observed from figure 5-11 that migraine was the class with less error, compared to TACs that registered the largest error rate.

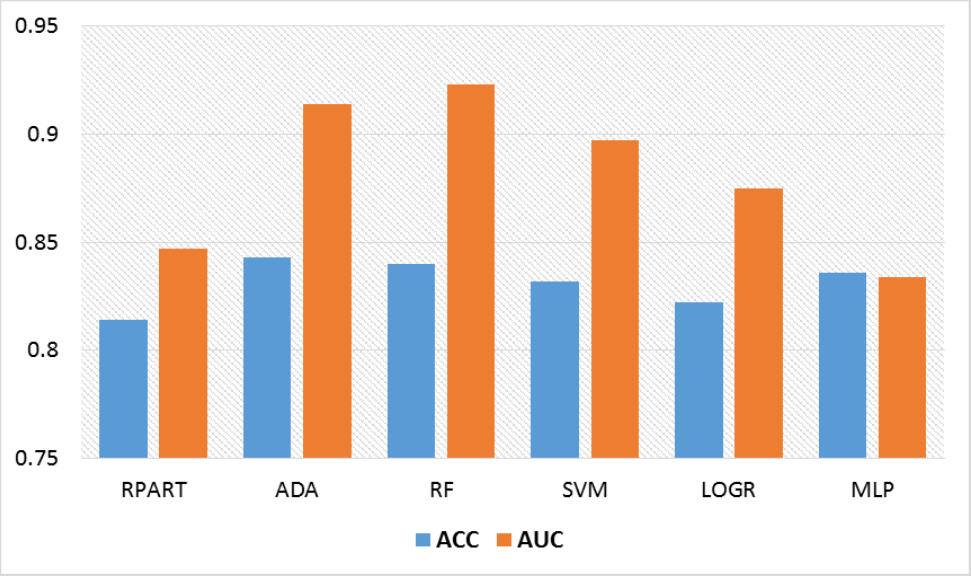


Figure 5-13: Pooled ACC and AUC

On the other hand, almost all of the predictive models, with the exception of the MLP learner, achieved AUC values that were noticeably higher than their overall classification accuracies as presented in figure 5-13. The MLP model shows a relative balance of values of AUC and ACC. The highest overall accuracy was achieved by the ADA model with a value of 0.843, while the highest AUC value was about 0.92 and achieved by RF model.

In total, the results illustrate that machine learning represents an encouraging and viable approach for the diagnosis of primary headache disorders. The classification and regression tree RPART shows somewhat stable results in terms of the performance metrics. RPART model uses the ratio of information gain as a splitting criterion. The best spilt would minimise the impurity of the output data subsets. From the resulting subsets, the splitting process is repeated until a stopping criterion is invoked. In this study, a minimum number of observations that were selected as a stopping criterion are 16, which means that next split will not occur unless there are 16 observations in a leaf node. We have also identified an equal prior probability for each type of headache. In the RPART model, a predefined control parameter, i.e. complexity parameter or CP, can ensure an optimal tree size. RPART was the model that requires significantly less training time than other models. RPART model is a

non-linear supervised learning method that is typically used to classify non-linearly separable data and can be graphically represented as a binary decision tree. Figures 5-14 shows an example of RPART model for diagnosing of migraine.

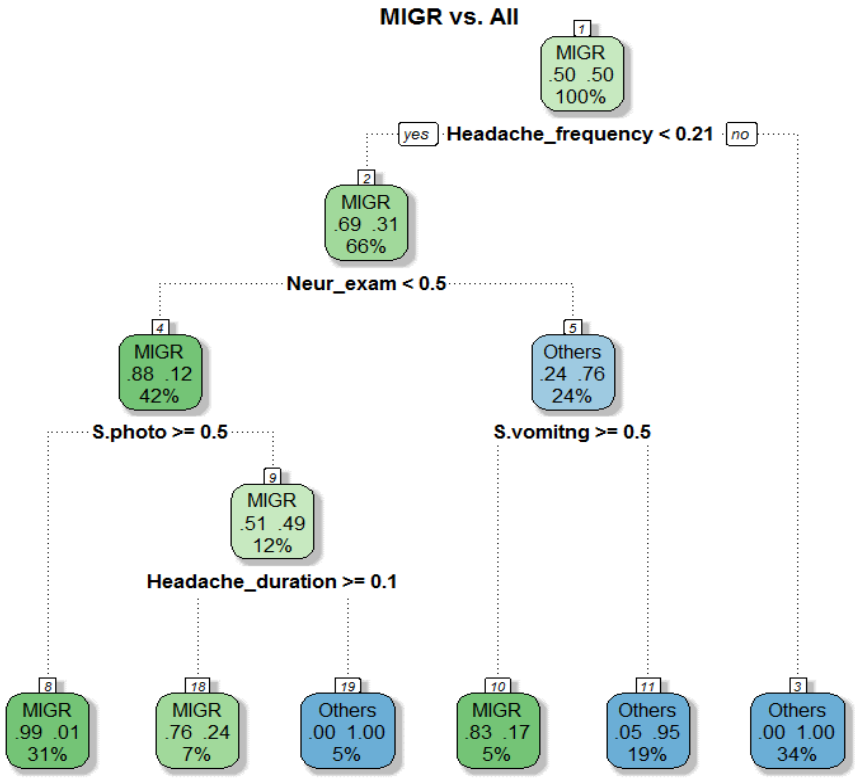


Figure 5-14: RPART model of migraine vs. all

Compared to the other predictive models such as MLP and SVM, RPART model has the advantage that it is not a black-box model. RPART model can be interpreted and expressed as a decision rules that derived from the data features as presented in table 4-12. Moreover, the interpretation of RPART model allows for an external validation by medical professionals. Barlin and others [151] have mentioned that RPART can manage highly skewed data, while it does not require many inputs compared to other multivariate modelling methods such as multivariate regression. On the other hand, the primary downside of the RPART model as highlighted by Dreiseitl and his colleague [152], is given by the greedy construction method, where at each splitting process, a single feature with optimum split-point is recruited. However, a multi-step look ahead that takes into account combinations of features might achieve much better results. In medical applications, the advantage of RPART model may carry more weight than its downsides [152]. However, RPART model does not ordinarily have the best overall performance when compared to other predictive models.

Therefore, ensemble learning has emerged to improve the performance of a singletree model via the use of many trees, then aggregating the predictions across these trees. Examples of ensemble learning method are random forest (RF) and adaptive boosting (ADA) models.

Table 5-12: The translation of figure 4-16 into a set of rules

Rule no.	Probability	Covers	Type of headache	Conditions
3	1.00	57(34%)	Others	Headache frequency >= 0.215
19	1.00	8(5%)	Others	Headache frequency < 0.215 Neurological exam < 0.5 Photophobia < 0.5 Headache duration < 0.105
11	0.95	33(19%)	Others	Headache frequency < 0.215 Neurological exam >= 0.5 Vomiting < 0.5
18	0.76	12(7%)	Migraine	Headache frequency < 0.215 Neurological exam< 0.5 Photophobia < 0.5 Headache duration >= 0.105
10	0.83	8(5%)	Migraine	Headache frequency < 0.215 Neurological exam >= 0.5 Vomiting >= 0.5
8	0.99	52(31%)	Migraine	Headache frequency < 0.215 Neurological exam< 0.5 Photophobia >= 0.5

RF model is a collection or ensemble of decision trees (DTs). RF takes the concept of DT a step further via generating dozens of trees. In contrast to DT, which uses all of the features along with the whole dataset to build a predictive model, RF selects an arbitrary sample of the data and determines a particular subset of features to build each DT individually. The resulting collections of DTs have their Out-Of-Bag error (i.e. OOB or error rate of the whole model) as shown in figure 5-16. This ensemble of DTs then compared to discover the best subset of features that can generate the most effective predictive models.

Our RF model built 100 separate DTs with m features considered at each split. In typical RF model $m = \sqrt{p}\ or\ log_2 p,$ where p is the number of the headache

features. The OOB estimate of error of RF model tends to decrease as the number of trees increases. We can also note that migraine was the class with less error, compared to TACs that registered the largest class error. Moreover, we can see the most importance features in the RF model through the mean decrease Gini as shown in figure 5-16. Gini measures the mean gain of purity by splits of a particular headache feature. When the feature is informative, it is likely to split mixed labelled headache nodes into pure single headache nodes.

The final RF model has identified that headache frequency, duration, location and characteristics are the most important features for the classification of primary headache as presented in figure 5-16. Although the RF model was slower when compared to the RPART model, which is the main drawback of the RF model, however, it was more accurate than RPART and tremendously reduces the chances of over-fitting that typically occur with a single deep DT via building smaller trees using random subsets of features [118]. In contrast to RPART, final classification of RF model is difficult to interpret as it is made by aggregating the classifications of the ensemble, where the model considers majority vote by the trees.

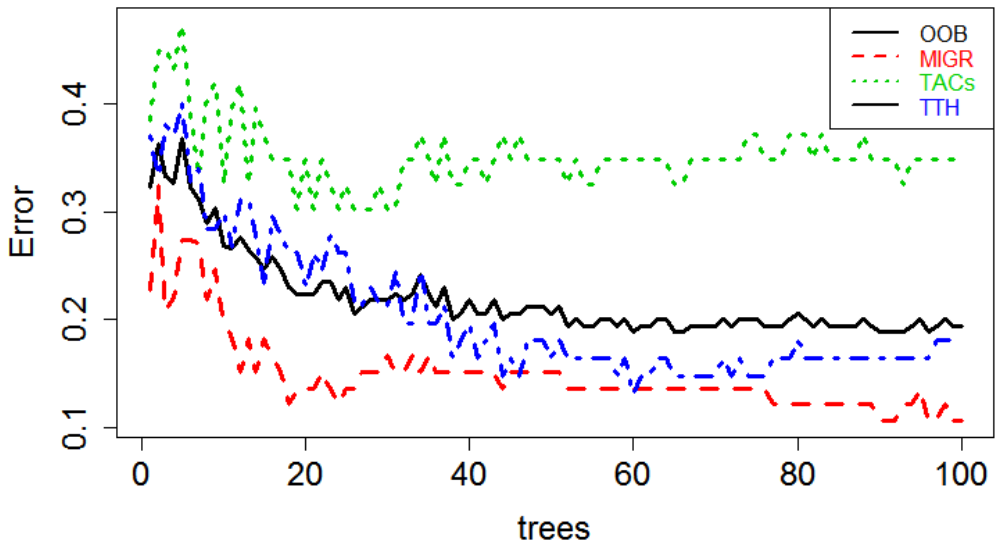


Figure 5-15: Class error rate of RF model with 100 trees

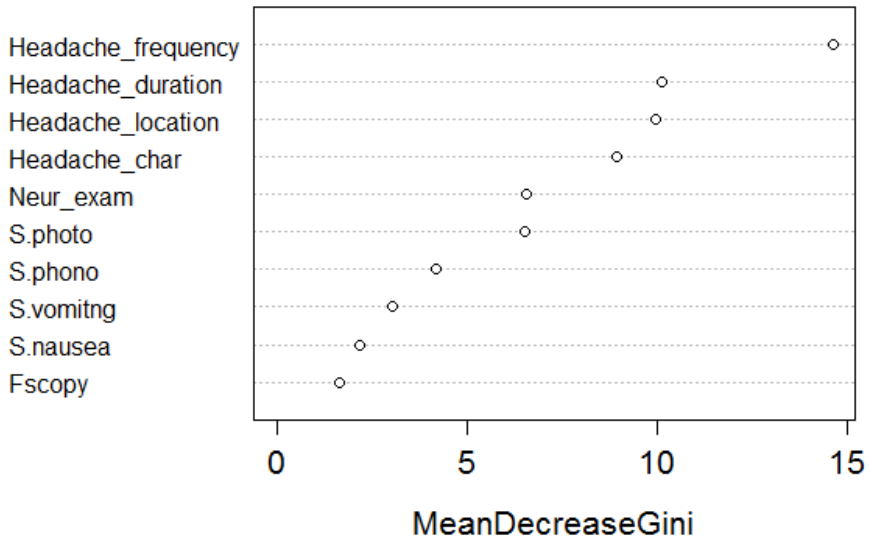


Figure 5-16: Features importance plot by RF model

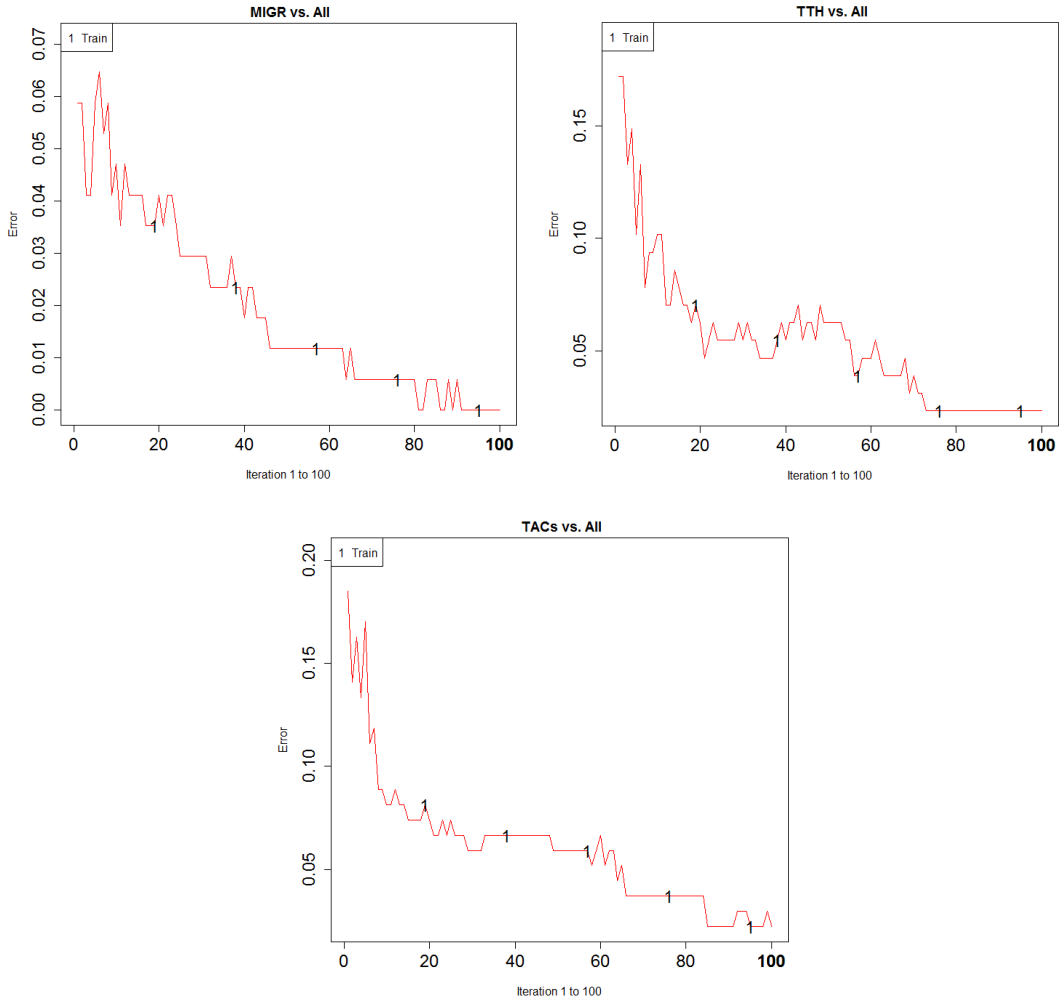


Figure 5-17: Training error of ADA model over a 100 iterations

Similarly, ADA model is another ensemble method that is used to boost the performance of any binary machine-learning classifier. This study uses the ADA learning method to boost the performance of RPART by creating a strong classifier from a number of trees, where the final classification of the ADA model is made by calculating the weighted average of the trees [153]. A single DT produced by the RPART model has a test error rate of 11%, 22% and 23% for headache classes of migraine, TACs and TTH respectively. In this context, the ADA model considerably drives down the training error, where after only forty iterations; the training error has dropped to less than 2%, 5% and 8% for migraine, TTH and TACs respectively. The test performance of the ADA model on the headache dataset was extremely good for all of the performance metrics, more stable than the RPART model and even than the RF model.

Away from tree-driven models, we have implemented two black-box models, i.e. SVM and MLP models, in addition to LOGR model. A 10-10-1 MLP neural network architecture shows the highest sensitivity with a very good predictive power with respect to the diagnosis of primary headaches. In contrast to all other models, MLP achieved a stable ACC and AUC values. However, the output of the MLP model might be more difficult to interpret when compared with tree-driven models, or even with LOGR model that allows a simple calculation of the probability of an output using the regression equation. Moreover, MLP is a computationally expensive model compared to LOGR models. For 10 headache features, MLP with one hidden layer requires significantly more parameters to estimate the output than LOGR models require. For example, MLP requires 131 connection weights with respect to migraine class, while LOGR takes only 10 coefficients to predict the same output.

Jack V. Tu in his thorough comparison [115] stated that the LOGR model can be disseminated to a considerably wider audience than the MLP model can. He attributed this issue to the fact that the connection weight matrices of the MLP model have occasionally been published and these matrices are most likely to be huge and difficult to interpret. Conversely, the coefficients of LOGR model are simple to interpret and use by end users to calculate the predicted likelihood of an outcome [115]. Additionally, Dreiseitl and his colleague [152] have stated that the wide use of LOGR and MLP models could possibly be encouraged by the advantage that they

have lower generalisation error than tree-driven models, meanwhile being simpler to develop than the SVM model.

The SVM model, on the other hand, is one of the dichotomous, kernel-based learning methods that the OVA approach extends its functionality to multi-class classification. The MLP model uses back propagation algorithm to adjust the weights and determine the set of weights and bias values with the goal of minimising error rate. In contrast, the SVM model in this study uses a Gaussian radial basis kernel function (RBF) to map the data into high dimensional space, where it is easier to create a linear decision boundary in the headache features space. The decision boundary, also called hyper-plane, should maximise the margin between the headache classes for an optimal diagnosis. SVM model with 70 support vectors has achieved a training error of 0.04 with respect to migraine class. Although SVM and MLP models behave differently, they are able to handle complex nonlinear relationships between the headache features and the outcome diagnosis when they exist. The hidden nodes within the MLP model allow the network to model complex nonlinear relationships, while different kernel functions, e.g. polynomial function, can be adopted by the SVM model to turn a linear model into a nonlinear model. In the context of nonlinearity, these models are more flexible and adaptable compared to the LOGR model. However, MLP, SVM and LOGR models are more complex for external validation than tree-driven models. Even though all of the predictive models have achieved impressive overall results in terms of performance metrics, however, we should be aware of individual variations, as shown in table 5-13, including advantages and drawbacks of adopting each one of the models by considering their capabilities on the truth ground.

Table 5-13: Comprehensive comparison of predictive models

		Predictive models					
No.	**Advantages**	**RPART**	**ADA**	**RF**	**SVM**	**LOGR**	**MLP**
1	Overall performance	🟢	🔵	🔵	🔵	🔵	🔵
2	Nonlinearity handling	🔵	🔵	🔵	🔵	🟡	🔵
3	Simplicity of interpretation	🔵	🟢	🟢	🟠	🟡	🟠
4	External validation	🔵	🔵	🔵	🟠	🟠	🟠
5	Computational complexity	🔵	🟡	🟡	🟠	🔵	🟠
6	Consider Features combination	🟠	🔵	🔵	🟢	🟢	🔵
7	Multi-class handling	🔵	🟠	🔵	🟠	🟠	🟠
Symbols: 🔵 very good; 🟢 good; 🟡 acceptable; 🟠 poor;							

5.8. Chapter summary

In this chapter, we have selected the most relevant subset of features using a majority vote of three different feature selection methods. This step was essential for a proper learning and generalisation approach, and at the same time to ensure reliable results. At the pre-classification stage, we have also analysed the nominated subset of features in order to investigate their discriminatory power in differentiating between different types of headaches. Also in this stage, we investigated the balance of class distribution to avoid any potential skewness of classifiers toward the majority class. Next, we have reviewed several statistical measures that have been used for the evaluation of the classifiers' prediction performance. Finally, we have trained and tested six supervised ML classifiers in OVA approach to create six predictive models for classification of primary headache disorders. The results of evaluation using OVA approach have been pooled in order to provide an overall comparison of predictive models, then generating a comprehensive picture that shows the advantages and disadvantages of each predictive model. We concluded this chapter with an extensive discussion that covers not only the predictive performance of these ML classifiers, but also highlights their capability in many aspects including computational complexity and error rates, handling of nonlinearity feature in data, simplicity of interpretation and capability of external validation by medical experts.

CHAPTER 6: HEADACHE FOLLOW-UP

6.1. Introduction

Nowadays, technology is widely adopted for healthcare delivery, which has made the healthcare system far better in several ways. Take for instance the Manchester Triage System (http://www.triagenet.net/), which is a clinical risk management tool used in emergency departments by clinicians to help in triaging patients. Many other computer tools intended for patients or managing appointments have been in use for decades to support healthcare. Although great improvements were made, however it goes without saying that technology to support the healthcare sector is always in need of more improvement. Therefore, the Department of Health, in 2012, reported that general practitioners (GPs) might soon direct their patients for free or affordable apps to involve themselves in managing their health more effectively [154]. After that, a call to find new ideas or existing smartphone apps that help patients and doctors in providing better healthcare has been announced. Many entries have been received including apps to manage diabetes, apps to monitor blood pressure, apps to help people with post-traumatic stress, apps to provide information about healthy diets and keeping fit and finally apps to find NHS services on a map. In this chapter, we introduce the HydroApp system to support self-management and follow-up of headaches as primary or secondary due to hydrocephalus.

6.2. The HydroApp system

HydroApp system is a web-based management, administration, communication and m-health application that provide follow-up treatment for patients with chronic headache or hydrocephalus. Using HydroApp, patients will be able to record all the pain events and the episodes related to those events, as well as access a quick and convenient way to fill in diaries, outcome measures and health questionnaires. Clinicians will have a central point of control, where the data will be collected from the patients' mobile app, analysed and presented in numerical and graphical formats. An inbuilt alert model will inform clinicians if there is any episode that may cause a serious situation. The HydroApp system is an end-to-end solution that allows information to flow smoothly between patients and clinicians.

As administrators, clinicians can create a unique patient profile, configure the type of condition, assign a condition to the patient profile and append any historical information such as previous diagnosis and medications. When this occurs, patients can begin using the HydroApp system and record all their episodes, and fill in diaries and outcome forms. Clinicians now are in a position to observe their patients' episodes and get updates. Patients will feel safer by realising that their clinicians are observing them and that they have an easy and efficient way to get in touch if necessary. The HydroApp system will provide clinicians with much more details about their patients on the day they have to visit the healthcare facility, and clinicians will be well prepared to manage their patients more efficiently, as well as making faster and better decisions. Lastly, the healthcare system, in general, could save money because clinicians can work faster and more efficiently in managing patients, as well as reducing avoidable visits to the healthcare facilities. This makes the solution very powerful and flexible by bringing the focus on self-management.

6.3. HydroApp system architecture

System architecture is the process of defining a structured solution that meets all the technical and operational requirements in order to identify how logically the system performs all the tasks. A modern web application needs to be scalable, reliable, ensure fast performance and be highly available, either if it is self-hosted or on the cloud. To achieve these features, HydroApp system has been built on a typical 3-tier architecture (figure 6-1). This architecture is the widely favoured architecture of modern web-based systems because it ensures a logical separation of all the required components to run the system. The front-end tier represents a client application. End-users (e.g. patients) operate on this tier and they know nothing regarding the other two tiers. At this tier, users can see the application through the graphical user interface (GUI), data will be captured from patients' mobile app and multiple views of the database can be provided to the clinicians via web application.

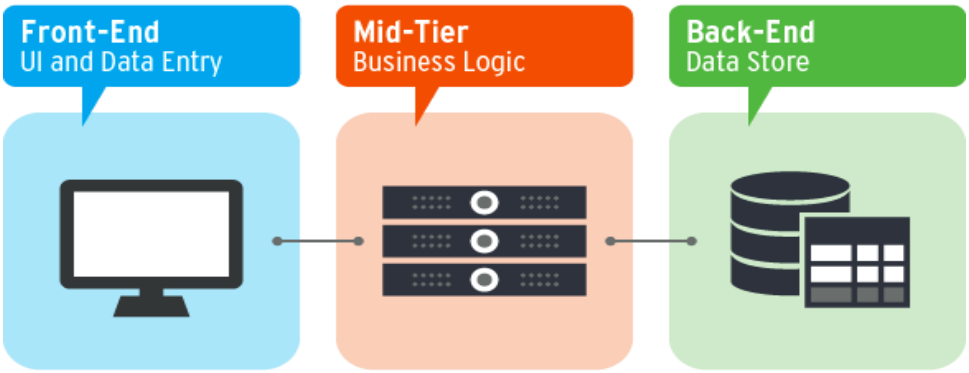


Figure 6-1: Simple overview of 3-tier applications

The business logic is the middle tier, which represents server application and programs that access the database (i.e. business logic and algorithms that process the data). For a user, this tier presents an abstracted view of the database. End-users are unaware of any existing database beyond the application. On the other hand, the back-end tier (i.e. database tier) is not aware of any other user beyond the application tier. Thus, the business logic tier is located in between the front-end and back-end tiers and plays the role of a mediator between the end-user and the database. In other words, it controls application functionality by performing detailed processing.

Finally, the data tier contains database servers where data is collected and retrieved. This tier is responsible for data persistence mechanisms and data access layer. The data is stored independently from business logic or front-end tiers, but can be retrieved and passed back to the business logic tier for processing and eventually to the end user. Although the 3-tier system architecture is complex to build and time-consuming, however, it is easy to maintain and involves numerous advantages; first, a logical separation among tiers to enable a parallel development for tiers. Secondly, the scalability of architecture allows the deployment of server application on multiple cloud platforms. Third, the middle tier (i.e. business logic) ensures a more secure environment by verifying and validating the data and preventing a direct access to the database. Moreover, the middle tier represents a protection shield for the database, where we can define new validation and protection rules without affecting the front-end tier. Figure 6-2 illustrates the big picture of the HydroApp system.

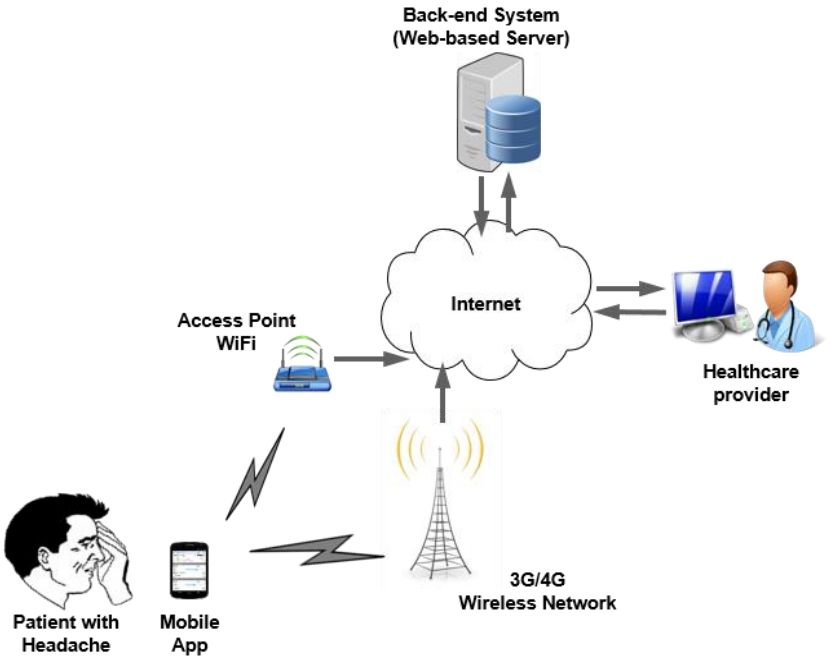
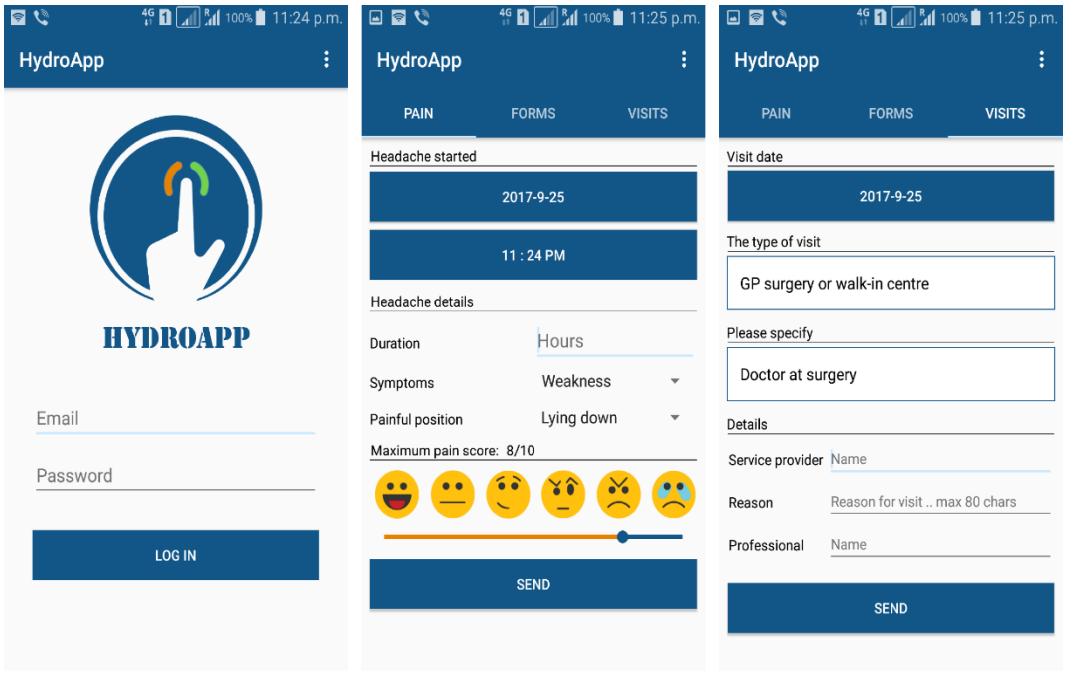


Figure 6-2: The big picture

6.3.1. The client application

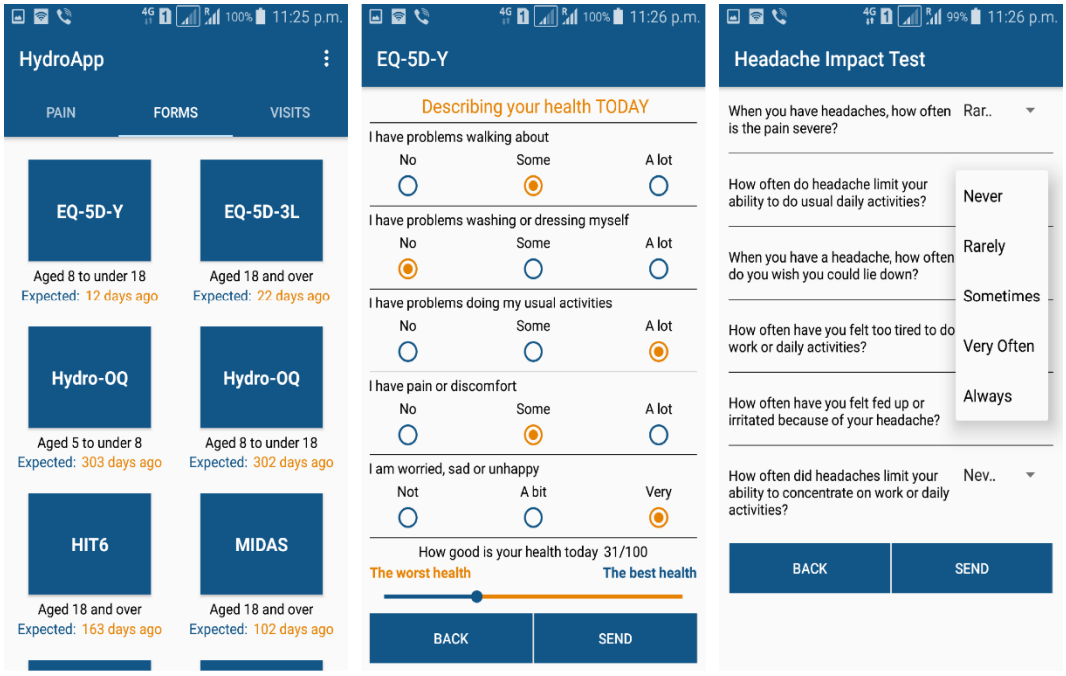
The client application (i.e. HydroApp) as shown in figures 6-3 and 6-4, is currently implemented using JAVA programming language for Android platform and it is independent from the server application, but they are communicating with each other via HTTP protocol. The client application can also be implemented for any other platform such as iOS or web-based application and communicate with the server application as long as it is capable of HTTP communication. The mobile clients will exchange data with the server via HTTP requests. In order to get or save the information needed such as reporting pain events or sending monitoring forms, clients will use the URIs that each resource in the web service has.

Prior authentication via a secure login system is required for the mobile client to use the service and be able to communicate with the server application. The clients must be connected to the internet via Wi-Fi or cellular network when required to send data. This solution might change in the future on mobile clients and desktop clients by applying a synchronization method, in which the data is stored locally and in the cloud, and then updated whenever the clients and server are online. This will enable users to send their data offline and synchronize when the client is online. This feature is out of scope for this first version of the project.



A: Login activity **B: Pain tab** **C: Visit tab**

Figure 6-3: HydroApp screenshots 1



A: Froms tab **B: EQ-5D-Y** **C: HIT-6**

Figure 6-4: HydroApp screenshots 2

6.3.2. The server application

The server application will run on a web server and connect to data tier (i.e., central database); these two tiers will be hosted on AIMES data centre (http://www.aimes.uk/), which provides hosting services to health and NHS business partner organisations. The server application will be a RESTful API and will query the database to serve and store the data to and from the clients. For more information about RESTful APIs, see REST API Guide by Oracle [159]. The server application must be scalable and able to handle potentially thousands of users. We developed the core of the server application using PHP5, JavaScript, while HTML and CSS are used to implement the GUI as shown in figures 6-5 and 6-6. The application server will verify the data sent from the mobile client before storing to central database.

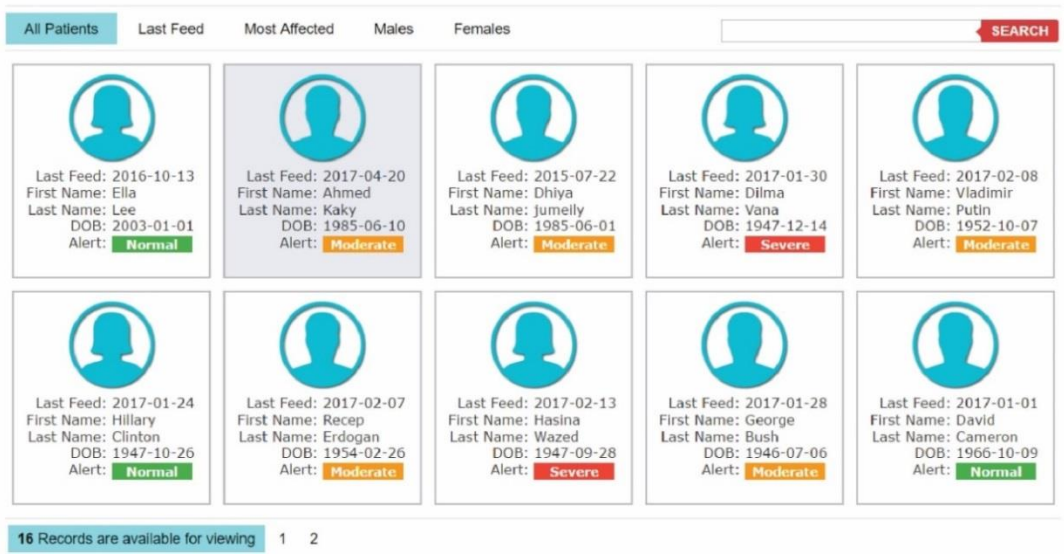


Figure 6-5: Example of patients profiles

Figure 6-6: Dashboard to present patients' data

6.3.3. Central database

The database is developed using MySQL database - InnoDB engine. We have designed the database in a way that can migrate to different database engines or a new table can be added for any new outcome forms when required. It will make use of SQL statements to query and populate the database. The RESTful API will have resources, which will make use of the database implementation to read/write data from and to client applications. To access the resources, the mobile app will use the embedded URIs.

The database design is very important for the system to work as intended, because we need to store and retrieve data dynamically, as well as adapt the clinician and patient user interfaces to this dynamically added data structure. Therefore, we adopt the star schema architecture in the development of the central database. The star schema is the simplest data warehouse schema and the most common nowadays, the diagram of the database resembles a 'star' with points radiating from a centre. In

order to make the database schema readable, we will logically group database tables into two sets of tables. The first set receives data from mobile clients while the second set receives data from administrators, both via server application.

Figure 6-7 shows the set of tables that feed the mobile clients; we will call this set of tables apps' tables. The centre of the star schema will be a login table, where the login details of clients are kept, while each one of the dimensional tables represent a monitoring form, pain diary or an assistant table. The star schema is simply a relational model. One-to-many relationship is defined from login table to eight dimension tables and One-to-one relationship to *patient_info* table that is initialised first by the administrator and *forms_time* table that stores dates when the monitoring forms are due. All tables are linked by *patient_id*, which is a unique integer identifier (key) generated by the system for each patient when the patient profile is setup.

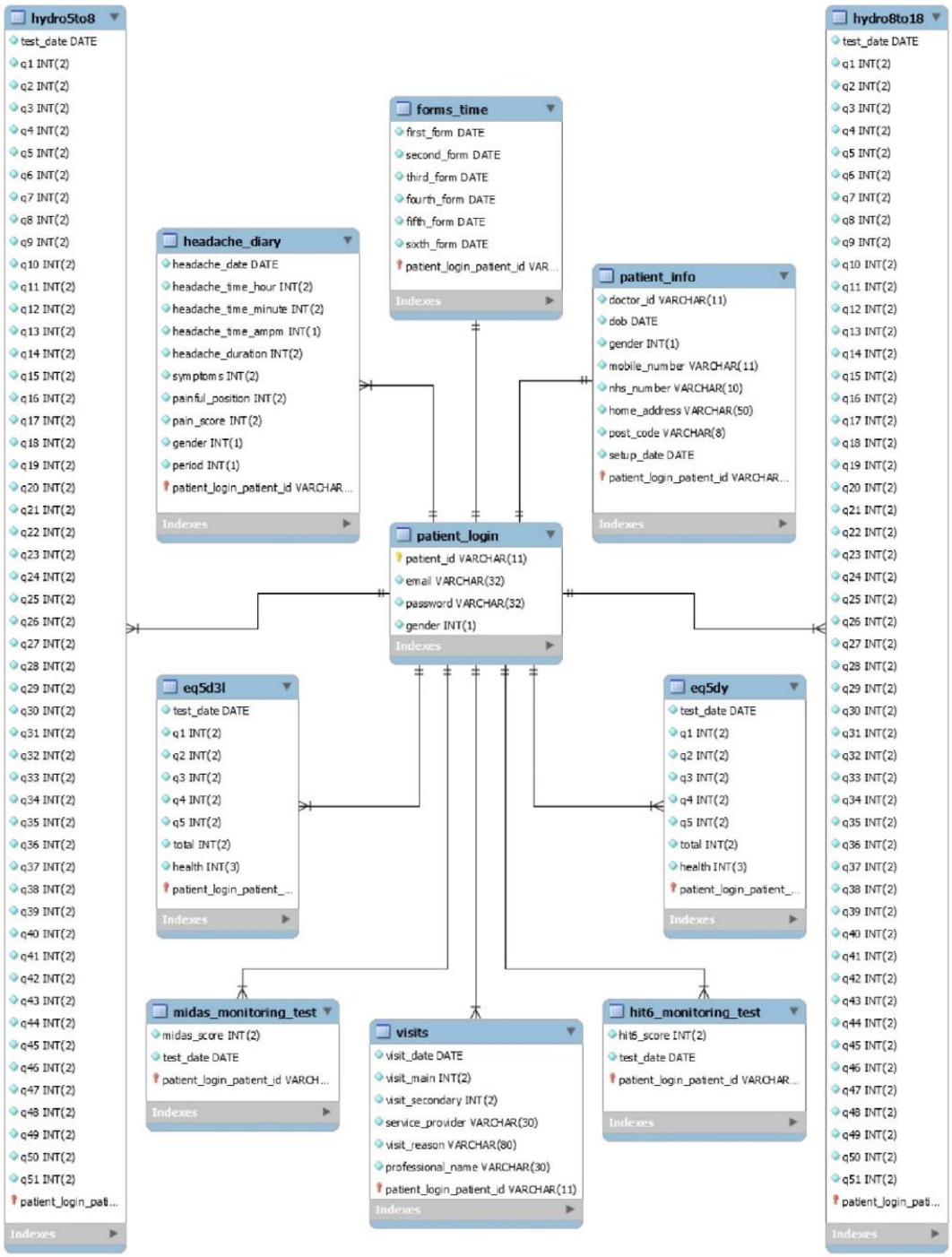


Figure 6-7: Star schema of Apps' tables

6.3.4. Data privacy and security

Data privacy and security are essential aspects that are required to be highly considered in data driven systems to ensure an adequate protection of clients' data. This section covers the security considerations that have been taken into account to protect the system and patients' data. On one hand, the central database and server application will be hosted on AIMES data centre, which provides secure hosting

services to a range of organisations, including the Health, pharmaceutical, automotive, professional services and the digital and creative sectors. AIMES meets the NHS criteria for information security and governance and is currently hosting data for The Institute of Child Health and Liverpool Heart and Chest Hospital. In addition to this, the central database will include anonymised data. Patient profiles will have no name or personal details that may expose patient identity. Furthermore, all collected data from mobile clients will be stored in numeric format rather than plain text for many reasons; first, the numeric representation will not provide any details about clients. Second, only the server app can display this representation into understandable format. Finally, it requires much less storage space and query time.

On the other hand, as we are managing the client accounts, the most important aspect is to protect client passwords. Instead of encoding passwords using Base64 method, which can be easily reversed to get the plain password, we protect client passwords using a salted password hashing method. Hash algorithms are one-way functions. They convert any quantity of data into a fixed-length "fingerprint" that cannot be reversed and will be completely different with any tiny variations in input. Theoretically, using hash functions is an ideal way to protect passwords because they are designed in a way that it is impossible to turn a hash code back into its original string. Storing passwords in a form of hash code will protect them even if the password file itself is compromised.

However, there is always a probability that malicious software and hackers may try to guess the passwords using pre-calculated dictionary attacks or brute-force attacks. Therefore, we use a process called "salting", which is a process of adding a random string called a salt to the password before the hashing process. This helps to lower the probability that the hash code maybe found in any pre-calculated table. Finally, to push the password protection level to the highest possible, we adopt a combination of hash functions in addition to adding salt in a process called two-step hash.

6.3.5. Authentication and authorisation

Authentication is a process of verifying clients through their provided credentials. In HydroApp system, we follow the common method of authentication, in which the clients will submit their login credentials (i.e., user names and passwords) via their mobile apps. The server application will receive a login request along with clients'

credentials. At first, the server application will validate the credentials and then query the table that includes the credentials of authorised users in order to find the same credential. If there was a match, the client is granted authorisation for access, otherwise the access will be denied. The passwords are not only encoded in the database, but they are transmitted from client app in encoded format as well. Therefore, passwords will never present in plain text in the system. The server application will send *patient_id* to the client app in order to start a session when the credentials are approved as illustrated in figure 6-9. The server application will respond with a general error message whether or not the username or password was incorrect. This can prevent enumeration of username and password by hackers. The majority of error messages generated as error code in server app are based on requirement and delivered to and expressed in the mobile client.

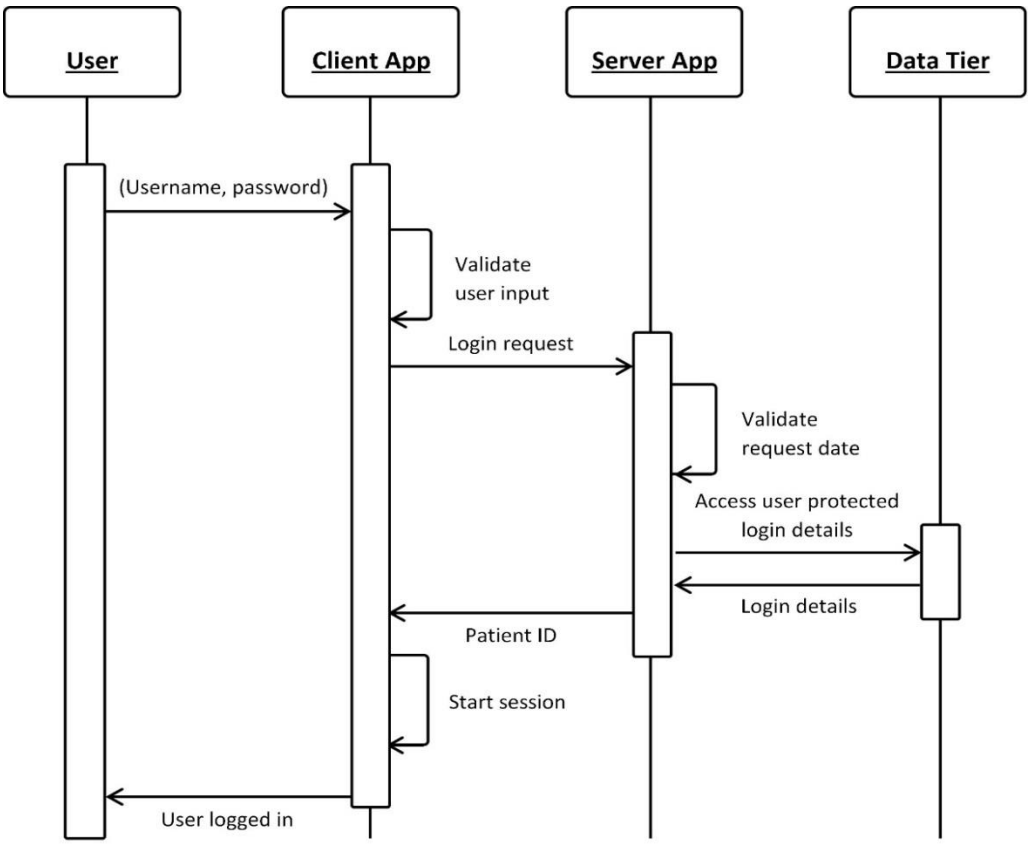


Figure 6-8: Authentication process

6.3.6. Application usability

The mobile App corresponds to a data collection component together with the responsibility of linking patients with the server application. A user-friendly mobile app would be an essential data source, intended to obtain the data directly from the patient, this would facilitate the collection of non-measurable signs or symptoms such as headache severity, pain location and feeling. As the system interacts with the patient directly, the user interface (UI) must be clear and intuitive, it must have a modern look and it must be fully featured and easy to use on mobile clients. We considered a patient's convenience through minimising data entry fields and taking advantage of alternatives such as, yes/no questions, pre-defined options, providing min and max attributes for input elements such as durations, date and so on.

6.4. HydroApp system in use for clinical follow-up study

We developed HydroApp system in accordance with the requirements of headache and hydrocephalus specialists at Alder Hey Children's NHS foundation trust and Walton centre - Liverpool. The HydroApp system meets their requirements of follow up, data collection and analysis. This is mainly because the HydroApp system includes a range of patients' self-reported outcome measures and monitoring forms as shown in figures 5.3 and 5.4 such as headache impact test (HIT6), hydrocephalus outcome questionnaire (Hydro-OQ), EQ5D-Y and EQ5D-3L, in addition to headache diary and visiting reports as shown in figure 6-3 and 6-4. Therefore, the BASICS clinical trial team is going to use the HydroApp system to extend the follow-up phase of the BASICS clinical study from two to ten years. BASICS (The British Antibiotic and Silver Impregnated Catheters for ventriculoperitoneal Shunts) is a randomised control trial (RCT), designed to compare the outcomes of children and adults diagnosed with hydrocephalus who have been randomised to receive Bactiseal (antibiotic impregnated VPS), or Silverline (silver impregnated VPS), versus the Standard VPS (made of silicone). The BASICS trial patient cohort is the largest cohort of shunted hydrocephalus patients ever studied prospectively worldwide, including 1600 patients.

The main objective of BASICS is to establish which shunt catheter is most effective in reducing shunt infection and within this context; the economic question is to assess which of the three shunts is most cost-effective for the NHS. Using HydroApp

system for collecting 10-year data on patients recruited to BASICS offers the opportunity to measure longer-term neurological outcomes, complications resulting from multiple shunt revisions and reductions in morbidity and infections. A long-term follow-up study should lead to a better understanding of the resource and healthcare implications for these patients and for the NHS to help plan and resource healthcare services for the future.

Most regional neuroscience centres follow-up large cohorts of shunted patients from within and outside of their region, often for the remainder of their life with little evidence-base for how and when they should be seen as out-patients or consideration for the huge burden on the patients and their families in terms of travel, time off work, school etc. The understanding that 'once a shunt, always a shunt' implies that nearly all patients, once implanted for hydrocephalus, will remain shunt-dependant for life and thus need some sort of life-long follow-up and relationship with the regional neuroscience centre. Better follow-up information, in terms of resources used, time spent in primary and secondary care, health professionals consulted, total in-patient stay, will lead to a better understanding and future effective planning for future follow-up and resource utilisation.

Given that there are no economic evaluations of VP shunts, evidence of which shunt is most efficient is needed to ensure that decisions are made on robust grounds. While the two-year follow-up period offers evidence of cost-effectiveness in the short term, there may be time horizon bias, which can only be mitigated through extended follow-up. Published studies show that shunts fail in the first 12 to 24 months with a rate between 30-50% [160-164] after shunt surgery and this is due to obstruction, infection or mechanical failure. A study undertaken in the USA which conducted a retrospective analysis on a cohort of patients extracted from 10 years of hospital admissions and discharges between 1990 and 2000, showed that the cumulative complication rate after 5 years of shunt insertion was 32% and that children tend to have a higher complication rate than adults [165].

Collecting 10-year data on patients recruited to BASICS offers the opportunity to measure longer-term neurological outcomes, complications resulting from multiple shunt revisions and reductions in morbidity and infection. A longer observation period would allow for an assessment of how clinical organisation and patient

characteristics during the first two years shape individual trajectories in the medium and long term. The economic analysis will take the NHS and societal perspectives following NICE guidance. Healthcare costs will be collected for both arms of the trial in order to evaluate the burden that hydrocephalus has on patients and their families in the long term. Unit costs to account for patients' healthcare use and personal spending will be extracted from national sources. A cost effectiveness analysis will be run from the data collected in the follow up period and cost acceptability curves estimated.

The use of HydroApp system as a follow-up technique and data collection method will ensure that economic and patient-reported outcomes are recorded efficiently. It will be assumed that the standard use of such smartphone based PRO (patient reported outcome) and intelligent software will be able to reduce unnecessary visits to neuroscience centres, whilst enabling and improving communication between patient and neurosurgical care and follow by creating appropriate clinical thresholds for alerting medical staff to changes in symptoms or to changes of behaviours and of symptoms, automatically. Thus, it is improving safety whilst reducing unnecessary costs and speeding up communications and access when it counts.

Collecting outcome information from patients is critical for the success of a trial, but it can also be time consuming and expensive. A nested RCT Study Within a Trial (SWAT the use of smartphone for data capture) will allow us to test the hypothesis that patients' self-reported information using a smartphone app will provide more accurate, timely and economic data in comparison to paper questionnaires. Differences between the two groups will be tested using appropriate statistical methods (these will be specified once the pilot design has been finalised).

To initialise a pilot study, we have participated with the BASICS clinical trial team in developing an online questionnaire asking the recruited patients about their experience of living with a shunt and follow-up with the medical profession. In addition, we investigated the acceptance of using technology to manage living with a shunt and follow-up. As of this writing, we obtained 37 responses from hydrocephalus patients with VP shunts, in which 15 were adults and 22 paediatric patients. The mean age of adult and paediatric patients were 36.4 and 8.3 years respectively. Approximately 80% of paediatric patients had 1-4 shunt operations,

compared to 60% of adult patients. The majority of patients usually spent 30 minutes or less as a waiting time, while 5-6% had to wait up to 60 min. About half of the patients spent 10-15 minutes with the doctor or nurse in clinic, while it is very rare that patients only spend 5 min or less with the doctor or nurse in clinic.

One third of patients would like to be seen by the neurosurgery team in clinic every 6 months, while the other one third yearly. Surprisingly, 20% of adult patients prefer to be seen in clinic only when they have problems. In total, about 78% of all patients expected to be followed up routinely in clinic for life. On the other hand, and for participating in the use of technology to manage living with a shunt and follow-up, paediatric patients was more interested in taking part in such a study, where 86% of them said yes, compared to 60% of adult patients. All paediatric patients have smartphones, compared to approximately 79% of adult patients, while the majority of patients have a home computer with internet access. Patients who were interested in taking part in such a study have rated the listed aspects of using technology for follow-up as shown in table 6-1 as very or extremely important on a scale of 1 to 5 (i.e. from least important to most important).

Table 6-1: Very or extremely important aspects of using technology for follow-up

		Patients (%)	
		Adults	**Paediatric**
1	Record your headache score	93%	85%
2	Record your general health and well-being	69%	81%
3	Alert your treating team	85%	90%
4	Record and update your details about your shunt	62%	90%
5	Conduct a video-call appointment	46%	52%
9	Conduct video-call emergency consultation	43%	81%

It is obvious that the first four points listed in the above table, i.e. recording headache score and general health, recording details about the shunt and alerting the medical team, were seen by patients as the most important aspects in terms of using the HydroApp system for self-management and follow-up. In contrast, making a video-call in general was the less important aspect from the patients' point of view. On the other hand, eight patients were not interested in taking part in such a study (5 adults and 3 paediatric). Although they were not interested in taking part, however more

than half of them rated the aspect of recording the headache score as very or extremely important.

6.5. The benefits of HydroApp system

More than 15 million people in England have a long-term condition [155]. These people use a large proportion of healthcare services. Patients with long-term conditions such as chronic headache or hydrocephalus are usually asked to complete traditional paper-based diaries or monitoring forms on a regular basis, which enables specialists to monitor and evaluate their status. However, within publically funded healthcare systems such as the UK's National Health Service (NHS), long-term follow-up in specialist clinics is not currently possible for all patients with long-term conditions. In 2014, the Royal College of General Practitioners reported that over 34 million patients in England would be unable to get an appointment with their GPs, when seeking treatment. This is due to the continued decline of the NHS funding budget and dramatically growing demand to provide high quality healthcare services [156]. Consequently, ensuring the continuity of care for all patients with long-term conditions requires a switch from a classical model of care to a new model, in which patients with long-term conditions are encouraged to track their conditions and to play a vital role in managing their own care.

In this context, there is scope to improve patient monitoring and safety in the specialist clinics by employing mobile health (M-health) technologies. The M-health application represents an intelligent solution, and holds potential to replace traditional paper based diaries and monitoring forms. The M-health scenario is the use of mobile phones, pads or any other handheld devices to follow-up patients with chronic conditions [157, 158]. In this study, we have developed a novel mobile application based system (i.e. HydroApp system) to enable remote monitoring of patients with chronic headache or hydrocephalus. This application focuses on pain and other symptoms that patients may suffer and enables them to enter their own episodes and to have a diary to follow up on their condition. Moreover, HydroApp system allows doctors or any qualified medical staff to keep close track of patients and avoid unnecessary visits to the hospital by reviewing each of their patients' histories. Additionally, it is entirely configurable; we can add any other monitoring forms or modify the app to suit for any remote monitoring purposes, no matter what

the condition being treated is. The impacts or advantages of HydroApp system can be summarised in two main aspects as presented below:

A. Impact on patients:

The primary impact of this work is to improve patient monitoring and safety. Patients with chronic headache or hydrocephalus can be better equipped to manage their own conditions and to maintain a good quality of life. HydroApp improves monitoring of historical responses to therapies and recording of side effects. Patients can send their diaries or monitoring forms anytime/anywhere. This will help to alleviate concerns about normal events that occur and to put the patient's mind at ease about specific events that commonly occur after installation of a shunt. Patients will feel safer by realising that their clinicians are observing them and that they have an easy way to get in touch if required.

B. Impact on the NHS:

The potential of the developed system to healthcare providers is significant. HydroApp system provides an end-to-end solution that allows information to flow freely between patients and clinicians. It overcomes the need to physically collect and interpret data from remote facilities, such as the home, which can be a time consuming process, expensive and often impossible due to a clinician's existing work commitments. The HydroApp system can improve communication between patients, clinicians and healthcare service provider. This will help to monitor a larger number of patients than would be possible in the current service model. Using the HydroApp system, clinicians will have more details about their patients on the day they have to visit the hospital and will be prepared to manage their patients more efficiently, as well as making faster and better decisions. Economically, the HydroApp system has a potential to reduce avoidable expenses for the NHS by reducing unnecessary visits on one hand, and enabling clinicians to work faster and more efficiently in managing their patients, on the other hand.

6.6. Chapter summary

This chapter introduced the HydroApp system, a method for self-management of patients with long-term conditions such as chronic headache and hydrocephalus. Several different technical aspects have been covered in this chapter, including the client application, server application and central database. This chapter also discussed the security and privacy procedures that have been followed in the design stage. This chapter ends with reviewing the benefit of using the HydroApp system for patients' follow-up, and shows the potential implementation of this system in neurology clinics at Alder Hey hospital.

CHAPTER 7: CONCLUSION AND FUTURE WORK

7.1. Conclusion

In general, this work proposes the use of intelligent approaches to improve the quality of healthcare provided to patients with headache. We worked toward improving the quality of care via two main ways; the first way was to improve the diagnosis or classification of primary headache disorders at primary clinics using machine-learning methods, while the second way was to start an M-health based platform to facilitate the long-term follow-up and clinical management of patients with chronic headache at neurology clinics.

This research was inspired by the urgent need for a new pathway that could reduce the burden on the shoulders of NHS, and at the same time enhance the quality of patients' lives. In fact, the use of machine-learning methods as a diagnostic model could reduce the need for specialist assessment as they can learn from previously diagnosed patients to diagnose new cases. These machine-learning based diagnostic models could also be used to train non-specialist doctors to improve their decision-making procedure. Likewise, the personalised M-health application has a potential to improve the long-term monitoring of patients with chronic headaches and enables specialists to monitor a larger number of patients. A remote follow-up using M-health technology can promote the quality of care given to this category of patients as well as engaging them in their condition management.

To establish intelligent diagnostic models, an experimental procedure was undertaken in this study by training six popular supervised machine-learning classifiers using patients' records originating from three medical institutions in Turkey, containing over 800 cases of patients with primary headaches. This stage usually known as the knowledge acquisition stage, where classifiers learned, identified patterns and gained knowledge from patients' records in order to classify new headache cases. Thereafter we have tested the classifiers' learning and generalisation capabilities using a number of records that not been used in the training process, i.e. holdout method. Using a number of statistical measures, we have evaluated the classifiers' sensitivity, specificity and classification accuracy to establish a performance evaluation.

Generally, all of the predictive models have achieved impressive pooled results. The MLP model has achieved the highest sensitivity, followed by the ADA model with a sensitivity value of 0.86, then PRART and LOGR that showed somewhat similar sensitivities. The ADA model achieved the highest classification accuracy, while the highest AUC value was about 0.92 and achieved by the RF model. Almost all of the predictive models, with exception of the MLP learner, achieving AUC values that were noticeably higher than their classification accuracies. The MLP model shows a relative balance between AUC and ACC values. Migraine was the most accurately classified type of headache, and all of the predictive models have shown a balance between F1 and AUC values with respect to the diagnosis of migraine.

In addition to the performance evaluation, we have configured and started with a comprehensive assessment and comparison of the targeted classifiers using not only the performance matrices, but also considering their points of strengths and weakness such as the simplicity of model interpretation and capability of external validation by a medical expert. We have also considered their computational complexity, required training time and error rates. Moreover, we discussed and investigated the models' ability to handle multi-class problems and nonlinearity in data. In summary, the results reveal that intelligent systems, i.e. machine learning based diagnostic models, represent a promising approach for the classification of primary headaches, and are likely to hold significant prospects to improve traditional models of diagnostic delivery.

Likewise, patients with long-term conditions such as chronic headache and hydrocephalus can be better equipped to manage their own conditions using the proposed HydroApp system. We have investigated the acceptance of using such M-health based system for patients' follow-up via an online questionnaire. More than 80% of paediatric patients and about 60% of adult patients were interested in using the HydroApp system to manage their conditions. In general, over 80% of those who are interested, have rated the recording of their headache score, general health and well-being as well as alerting their treating team as very or extremely important aspects when using the HydroApp system. Some other aspects such as conducting video-call appointment and consultation were less important from the patients' point of view.

In aggregate, machine learning based diagnostic models in combination with the HydroApp system for long-term follow-up are likely hold a significant potential to improve the quality of healthcare provided to patients with headaches, and reduce avoidable expenses for the NHS by reducing unnecessary visits on one hand, and enabling clinicians to work faster and more efficiently in managing their patients on the other. In short, it is the start of personalised healthcare.

7.2. Future work

Although we have evaluated the diagnostic models using a part of the data set, however the diagnostic labels in this data might be inaccurate. Therefore in the future work, we aim to validate the diagnostic models in primary care clinics and by a number of headache specialists on the one hand, and installing and validating the HydroApp system with patients treated with VP shunts at Alder Hey hospital on the other. We also aim to overcome some of the key limitations inherited from patients' records. For example, a patient who presents with headache will be labelled with only one diagnosis. However, this should be extended to allow for multiple simultaneous diagnoses because multiple types of headache are known to coexist in the same patient, or a particular type of headache may transform into another one [166, 167].

Additionally, it is understood that the diagnosis of primary headaches is based on the history and examination, however, it is worthwhile to investigate whether genetic factors can play a role for an early prediction of headaches. Likewise, physiological signals like EEG may provide another channel of information to improve the diagnosis of headaches, where it may be possible that each type of headache has its hidden patterns in EEG signals. Finally, we can also recommend the use of other statistical and learning methods such as principle component analysis for dimensional reduction and deep learning algorithms, which may lead to better diagnostic results.

Appendix A: Separate Variance t Tests

Separate Variance t Tests[a]

		Age	Admission	Onset	Frequency	Duration	Smok.dur	P.killer	Movr.dur
Smok.dur	t	1.5	.5	-1.3	.1	-1.3	.	1.5	1.0
	df	147.2	147.3	157.6	140.4	162.9	.	6.0	4.0
	# Present	111	110	109	110	109	113	7	5
	# Missing	706	706	689	696	685	0	12	9
	Mean(Present)	46.919	38.009	73.725	10.455	18.01193	8.075	74.286	8388.000
	Mean(Missing)	44.677	37.309	84.218	10.365	20.95510	.	21.417	17.000
P.killer	t	-1.2	.6	3.2	-.5	2.0	.6	.	.
	df	19.9	19.7	18.3	19.8	19.1	9.5	.	.
	# Present	19	19	19	19	19	7	19	14
	# Missing	798	797	779	787	775	106	0	0
	Mean(Present)	42.158	38.684	192.632	9.632	31.42105	9.143	40.895	3006.643
	Mean(Missing)	45.049	37.373	80.106	10.395	20.28457	8.005	.	.
Movr.dur	t	-.4	1.2	3.0	.0	1.3	.6	1.6	.
	df	13.9	13.8	13.1	13.8	13.5	6.5	13.3	.
	# Present	14	14	14	14	14	5	14	14
	# Missing	803	802	784	792	780	108	5	0
	Mean(Present)	44.000	40.571	211.714	10.429	28.92857	9.000	48.714	3006.643
	Mean(Missing)	44.999	37.348	80.483	10.376	20.40069	8.032	19.000	.
H.intesity	t	1.8	-.6	-1.5	7.4	-3.2	-2.1	.	.
	df	82.0	81.3	77.2	99.3	45.7	6.0	.	.
	# Present	751	750	732	747	752	107	19	14
	# Missing	66	66	66	59	42	6	0	0
	Mean(Present)	45.210	37.329	81.320	10.765	19.85511	7.780	40.895	3006.643
	Mean(Missing)	42.379	38.242	99.030	5.466	33.01190	13.333	.	.
MH.acc	t	5.1	-.2	-3.2	9.4	-3.4	-2.7	.	.
	df	248.1	237.3	162.4	369.8	131.8	12.6	.	.
	# Present	682	681	667	677	674	102	19	14
	# Missing	135	135	131	129	120	11	0	0
	Mean(Present)	45.886	37.370	77.534	11.226	18.59502	7.436	40.895	3006.643
	Mean(Missing)	40.415	37.570	109.523	5.922	31.53750	14.000	.	.
MH.perv om	t	3.3	-1.3	-3.9	7.5	-3.8	-2.7	.	.
	df	232.9	226.3	170.1	313.8	145.6	12.6	.	.
	# Present	670	669	655	668	662	102	19	14
	# Missing	147	147	143	138	132	11	0	0
	Mean(Present)	45.710	37.123	75.492	11.183	18.25611	7.436	40.895	3006.643
	Mean(Missing)	41.660	38.680	116.192	6.478	32.06061	14.000	.	.
MH.msic	t	4.3	-.8	-3.7	7.5	-3.8	-2.7	.	.

k	df	256.3	246.8	169.2	297.8	140.3	12.6	.	.
	# Present	674	673	659	672	666	102	19	14
	# Missing	143	143	139	134	128	11	0	0
	Mean(Present)	45.810	37.250	76.253	11.162	18.28009	7.436	40.895	3006.643
	Mean(Missing)	41.077	38.126	113.752	6.440	32.36719	14.000	.	.
MH.abdpain	t	4.4	-.7	-3.7	7.4	-3.7	-2.7	.	.
	df	254.3	245.3	167.5	292.9	139.0	12.6	.	.
	# Present	675	674	660	673	667	102	19	14
	# Missing	142	142	138	133	127	11	0	0
	Mean(Present)	45.827	37.276	76.191	11.152	18.32465	7.436	40.895	3006.643
	Mean(Missing)	40.965	38.007	114.322	6.459	32.24409	14.000	.	.
MH.epil	t	3.4	-1.3	-3.5	8.3	-3.7	-2.7	.	.
	df	228.9	221.0	174.5	328.6	141.6	12.6	.	.
	# Present	673	672	658	671	665	102	19	14
	# Missing	144	144	140	135	129	11	0	0
	Mean(Present)	45.709	37.134	76.751	11.224	18.29706	7.436	40.895	3006.643
	Mean(Missing)	41.583	38.660	111.146	6.170	32.17054	14.000	.	.
MH.surg	t	3.7	-1.0	-3.6	5.7	-3.8	-3.1	.	.
	df	237.1	228.6	163.5	246.0	133.5	12.5	.	.
	# Present	678	677	664	676	671	102	19	14
	# Missing	139	139	134	130	123	11	0	0
	Mean(Present)	45.701	37.223	76.637	11.012	18.26012	7.338	40.895	3006.643
	Mean(Missing)	41.475	38.281	113.250	7.077	33.04878	14.909	.	.
MH.allerg	t	2.9	-2.0	-3.6	4.7	-3.6	-3.2	.	.
	df	303.4	296.5	191.9	283.9	161.3	14.9	.	.
	# Present	656	655	641	654	650	100	19	14
	# Missing	161	161	157	152	144	13	0	0
	Mean(Present)	45.599	36.992	75.651	11.002	18.31391	7.185	40.895	3006.643
	Mean(Missing)	42.466	39.075	111.914	7.691	30.64931	14.923	.	.
MH.homo	t	2.5	-2.4	-3.6	4.2	-3.3	-3.6	.	.
	df	327.5	319.4	214.2	307.1	178.5	17.4	.	.
	# Present	643	642	628	641	638	98	19	14
	# Missing	174	174	170	165	156	15	0	0
	Mean(Present)	45.555	36.866	75.600	10.992	18.43345	6.923	40.895	3006.643
	Mean(Missing)	42.862	39.385	109.326	7.988	29.21154	15.600	.	.
MH.stroke	t	3.8	-1.3	-3.9	7.4	-3.8	-3.5	.	.
	df	274.2	264.7	181.6	322.0	149.4	14.9	.	.
	# Present	666	665	651	663	659	100	19	14
	# Missing	151	151	147	143	135	13	0	0
	Mean(Present)	45.748	37.143	75.642	11.211	18.24968	7.085	40.895	3006.643
	Mean(Missing)	41.603	38.550	114.418	6.510	31.78519	15.692	.	.

MH.ather	t	3.9	-1.1	-4.1	7.6	-3.9	-2.7	.	.
	df	255.5	246.9	169.8	307.0	140.1	12.6	.	.
	# Present	673	672	658	670	666	102	19	14
	# Missing	144	144	140	136	128	11	0	0
	Mean(Present)	45.756	37.188	75.403	11.182	18.20352	7.436	40.895	3006.643
	Mean(Missing)	41.361	38.410	117.482	6.412	32.76562	14.000	.	.
MH.lipid	t	4.5	-.5	-3.8	7.7	-3.9	-2.4	.	.
	df	232.0	222.6	157.3	289.2	147.0	13.1	.	.
	# Present	683	682	668	679	676	103	19	14
	# Missing	134	134	130	127	118	10	0	0
	Mean(Present)	45.818	37.321	76.290	11.130	18.85583	7.655	40.895	3006.643
	Mean(Missing)	40.716	37.821	116.158	6.354	30.26271	12.400	.	.
Oral contraceptive	t	-5.5	-.3	3.8	-1.9	1.0	4.4	.	.
	df	733.4	718.0	678.4	734.6	791.2	76.7	.	.
	# Present	343	343	337	331	327	37	19	14
	# Missing	474	473	461	475	467	76	0	0
	Mean(Present)	41.816	37.251	97.111	9.637	21.54483	12.527	40.895	3006.643
	Mean(Missing)	47.272	37.514	72.312	10.893	19.85521	5.908	.	.
MH.hyper	t	-1.7	3.1	4.0	-.3	.8	2.7	.	.
	df	800.4	798.0	782.5	801.4	735.7	109.3	.	.
	# Present	400	400	394	391	387	51	19	14
	# Missing	417	416	404	415	407	62	0	0
	Mean(Present)	44.127	38.902	95.671	10.263	21.28887	10.324	40.895	3006.643
	Mean(Missing)	45.801	35.962	70.218	10.484	19.84951	6.226	.	.
MH.diab	t	-4.2	.6	3.4	-1.2	.8	3.1	.	.
	df	775.5	767.9	752.6	772.8	739.2	92.7	.	.
	# Present	368	368	364	358	355	42	19	14
	# Missing	449	448	434	448	439	71	0	0
	Mean(Present)	42.658	37.712	94.444	9.953	21.36688	11.060	40.895	3006.643
	Mean(Missing)	46.886	37.150	73.007	10.717	19.89134	6.310	.	.
MH.cadis	t	-4.8	.0	3.1	-1.4	.1	3.8	.	.
	df	767.2	757.0	738.7	766.1	775.6	89.0	.	.
	# Present	359	359	355	349	345	41	19	14
	# Missing	458	457	443	457	449	72	0	0
	Mean(Present)	42.290	37.412	93.877	9.854	20.62969	11.720	40.895	3006.643
	Mean(Missing)	47.092	37.396	73.896	10.777	20.49065	6.000	.	.
MH.snor	t	-5.5	-1.7	3.9	-10.6	1.2	3.0	1.3	.
	df	270.8	263.7	245.5	595.9	347.5	52.6	16.7	.
	# Present	173	173	168	170	161	23	17	13
	# Missing	644	643	630	636	633	90	2	1
	Mean(Present)	39.775	35.815	108.143	5.918	22.35901	11.565	43.059	32.462

	Mean(Missing)	46.380	37.830	76.023	11.569	20.09122	7.183	22.500	41671.000
MH.osas	t	-5.4	-1.7	3.7	-10.6	1.2	3.0	1.5	-1.0
	df	265.0	257.9	244.2	585.0	337.6	47.7	15.8	1.0
	# Present	171	171	166	168	159	22	16	12
	# Missing	646	645	632	638	635	91	3	2
	Mean(Present)	39.819	35.813	106.699	5.917	22.37610	11.727	44.813	33.167
	Mean(Missing)	46.348	37.825	76.504	11.552	20.09408	7.192	20.000	20847.500
Infantile colic	t	-6.5	-2.3	3.1	-5.9	-2.0	2.8	-.4	-1.0
	df	101.7	99.6	84.5	124.0	127.2	27.0	10.9	5.0
	# Present	74	74	74	73	74	16	11	8
	# Missing	743	742	724	733	720	97	8	6
	Mean(Present)	36.973	34.622	117.068	6.521	16.96216	12.125	35.182	20.250
	Mean(Missing)	45.779	37.681	79.281	10.761	20.91992	7.407	48.750	6988.500
Med.over	t	-6.9	-2.3	4.3	-12.8	4.0	3.2	.	.
	df	350.6	342.8	290.5	701.7	413.6	47.4	.	.
	# Present	190	190	187	184	187	21	19	14
	# Missing	627	626	611	622	607	92	0	0
	Mean(Present)	39.232	35.532	108.294	5.353	26.23369	11.857	40.895	3006.643
	Mean(Missing)	46.724	37.971	74.978	11.863	18.80040	7.212	.	.
FH.head	t	-4.7	-3.3	3.8	-4.8	1.3	2.6	.	.
	df	713.8	735.3	768.5	601.2	580.3	110.9	.	.
	# Present	481	481	470	472	466	60	19	14
	# Missing	336	335	328	334	328	53	0	0
	Mean(Present)	43.012	36.121	92.454	9.012	21.64086	9.942	40.895	3006.643
	Mean(Missing)	47.801	39.245	68.930	12.307	19.00275	5.962	.	.
FH.hyper	t	-4.6	-1.9	2.4	-3.8	.1	1.3	.	.
	df	794.7	791.9	792.5	802.5	762.0	109.0	.	.
	# Present	376	376	367	367	362	60	19	14
	# Missing	441	440	431	439	432	53	0	0
	Mean(Present)	42.500	36.431	90.812	9.038	20.60215	9.025	40.895	3006.643
	Mean(Missing)	47.098	38.234	75.950	11.497	20.50825	7.000	.	.
FH.atopic	t	-6.5	-1.8	3.8	-3.5	.9	3.9	.	.
	df	600.2	585.5	605.4	651.2	759.4	69.3	.	.
	# Present	295	295	290	287	285	33	19	14
	# Missing	522	521	508	519	509	80	0	0
	Mean(Present)	40.705	36.288	98.579	8.868	21.60930	12.318	40.895	3006.643
	Mean(Missing)	47.398	38.035	73.769	11.212	19.95853	6.325	.	.
FH.diab	t	-5.6	-1.9	2.9	-3.8	.4	2.3	.	.
	df	731.2	722.3	730.2	755.3	791.7	102.3	.	.
	# Present	339	339	332	330	326	48	19	14
	# Missing	478	477	466	476	468	65	0	0

	Mean(Present)	41.696	36.322	93.461	8.900	20.93942	10.135	40.895	3006.643
	Mean(Missing)	47.312	38.172	75.179	11.401	20.28054	6.554	.	.
FH.hdis	t	-5.3	-1.6	2.9	-3.6	.7	3.3	.	.
	df	700.2	696.1	706.1	748.1	790.9	77.3	.	.
	# Present	328	328	319	320	316	38	19	14
	# Missing	489	488	479	486	478	75	0	0
	Mean(Present)	41.768	36.494	93.978	8.984	21.28060	11.461	40.895	3006.643
	Mean(Missing)	47.137	38.014	75.331	11.294	20.06877	6.360	.	.
FH.epil	t	-6.2	-1.4	3.7	-3.5	1.4	3.9	.	.
	df	636.6	623.7	639.9	673.8	760.6	69.3	.	.
	# Present	304	304	299	296	292	33	19	14
	# Missing	513	512	499	510	502	80	0	0
	Mean(Present)	41.016	36.559	97.779	8.902	22.08613	12.318	40.895	3006.643
	Mean(Missing)	47.331	37.904	73.801	11.233	19.65815	6.325	.	.
FH.psych	t	-5.8	-1.2	3.3	-3.4	1.2	3.9	1.7	1.0
	df	607.2	586.5	619.9	647.0	748.1	56.6	16.7	11.0
	# Present	295	295	290	287	283	30	17	12
	# Missing	522	521	508	519	511	83	2	2
	Mean(Present)	41.166	36.620	96.524	8.920	21.95813	12.583	43.647	3502.750
	Mean(Missing)	47.138	37.846	74.942	11.183	19.77180	6.446	17.500	30.000
Smok	t	3.3	-.8	-2.6	10.3	-2.9	.	.	.
	df	131.4	127.1	103.3	217.6	94.3	.	.	.
	# Present	726	725	710	722	713	112	19	14
	# Missing	91	91	88	84	81	1	0	0
	Mean(Present)	45.460	37.295	79.487	10.987	19.54971	8.058	40.895	3006.643
	Mean(Missing)	41.165	38.264	109.398	5.137	29.36543	10.000	.	.
T.emostr e	t	2.8	.6	-2.1	2.7	-3.0	-1.0	-1.0	1.0
	df	48.5	47.8	39.6	43.7	38.1	1.1	1.0	11.0
	# Present	774	773	760	768	759	111	17	12
	# Missing	43	43	38	38	35	2	2	2
	Mean(Present)	45.270	37.461	81.016	10.528	20.01916	7.986	29.824	3486.750
	Mean(Missing)	39.791	36.372	118.158	7.329	32.08571	13.000	135.000	126.000
T.physact	t	3.1	-.4	-3.1	4.1	-2.9	-2.1	-1.0	1.0
	df	114.3	110.9	85.8	109.5	89.6	5.6	1.0	11.0
	# Present	733	732	719	727	718	108	17	12
	# Missing	84	84	79	79	76	5	2	2
	Mean(Present)	45.423	37.340	78.364	10.733	19.63411	7.884	29.824	3486.750
	Mean(Missing)	41.131	37.952	123.025	7.101	29.21382	12.200	135.000	126.000
T.menstr ual	t	.8	-1.7	-2.0	3.4	-1.6	-2.1	-1.0	1.0
	df	68.4	66.9	56.3	62.9	51.3	8.6	1.0	11.0
	# Present	760	759	745	754	743	108	17	12

	# Missing	57	57	53	52	51	5	2	2
	Mean(Present)	45.071	37.204	80.619	10.617	19.75241	7.940	29.824	3486.750
	Mean(Missing)	43.789	40.053	113.226	6.894	32.18627	11.000	135.000	126.000
T.season	t	3.5	-.3	-3.3	4.0	-2.4	-.8	-1.0	1.0
	df	141.2	136.1	101.2	130.5	104.6	4.8	1.0	11.0
	# Present	720	719	707	716	709	108	17	12
	# Missing	97	97	91	90	85	5	2	2
	Mean(Present)	45.519	37.363	77.876	10.756	19.78920	7.977	29.824	3486.750
	Mean(Missing)	40.990	37.701	120.923	7.367	26.90588	10.200	135.000	126.000
T.alcohol	t	-6.0	.1	3.3	-3.8	1.8	5.7	-1.0	1.0
	df	793.4	784.9	777.3	798.5	790.7	83.6	1.0	11.0
	# Present	371	371	366	361	355	43	17	12
	# Missing	446	445	432	445	439	70	2	2
	Mean(Present)	41.771	37.466	94.149	9.029	22.39482	13.128	29.824	3486.750
	Mean(Missing)	47.652	37.351	73.157	11.471	19.06010	4.971	135.000	126.000
T.skipmeal	t	-6.4	.5	4.7	-4.4	3.5	5.5	-1.0	1.0
	df	813.4	813.7	793.3	797.0	746.2	88.9	1.0	11.0
	# Present	407	407	402	394	387	44	17	12
	# Missing	410	409	396	412	407	69	2	2
	Mean(Present)	41.850	37.654	97.327	8.907	23.85313	12.875	29.824	3486.750
	Mean(Missing)	48.090	37.154	68.023	11.783	17.41126	5.014	135.000	126.000
T.posasso	t	4.4	.3	-3.5	6.3	-2.6	-1.8	-1.0	1.0
	df	156.4	151.1	112.6	183.0	116.3	11.6	1.0	11.0
	# Present	711	710	698	708	701	104	17	12
	# Missing	106	106	100	98	93	9	2	2
	Mean(Present)	45.702	37.449	77.260	10.903	19.65841	7.784	29.824	3486.750
	Mean(Missing)	40.151	37.094	121.350	6.577	27.27957	11.444	135.000	126.000
S.dizziness	t	4.6	.8	-2.8	5.1	-2.5	-2.1	.	.
	df	116.9	113.4	90.4	121.0	87.6	6.3	.	.
	# Present	732	731	717	727	720	108	19	14
	# Missing	85	85	81	79	74	5	0	0
	Mean(Present)	45.635	37.509	79.077	10.772	19.80422	7.912	40.895	3006.643
	Mean(Missing)	39.353	36.494	115.605	6.747	27.81757	11.600	.	.
S.sleepdist	t	3.7	-.6	-3.8	6.3	-3.2	-2.3	.	.
	df	173.8	167.2	125.0	204.4	109.9	12.8	.	.
	# Present	702	701	687	698	691	102	18	13
	# Missing	115	115	111	108	103	11	1	1
	Mean(Present)	45.641	37.291	76.212	10.954	18.75838	7.534	42.500	3237.692
	Mean(Missing)	40.957	38.087	123.468	6.648	32.57767	13.091	12.000	3.000
S.vertigo	t	1.6	-2.1	-2.6	1.7	-2.1	-2.9	.	.
	df	162.6	158.8	119.5	144.2	127.9	7.9	.	.

	# Present	707	706	692	702	695	105	19	14
	# Missing	110	110	106	104	99	8	0	0
	Mean(Present)	45.250	37.057	78.517	10.574	19.82308	7.424	40.895	3006.643
	Mean(Missing)	43.255	39.627	110.646	9.048	25.66162	16.625	.	.
	t	-7.5	-1.4	4.2	-5.5	3.4	4.6	.	.
	df	763.3	754.4	725.9	795.6	644.0	90.8	.	.
S.osmoph	# Present	353	353	347	343	338	39	18	14
	# Missing	464	463	451	463	456	74	1	0
	Mean(Present)	40.799	36.626	98.066	8.372	24.23272	12.372	41.778	3006.643
	Mean(Missing)	48.164	37.996	71.028	11.863	17.82211	5.811	25.000	.
	t	-6.8	-1.0	4.7	-5.2	2.7	3.7	.	.
	df	748.1	735.4	704.7	783.6	782.2	87.6	.	.
S.allodynia	# Present	346	346	340	334	330	35	19	14
	# Missing	471	470	458	472	464	78	0	0
	Mean(Present)	41.090	36.873	100.191	8.430	23.36109	11.757	40.895	3006.643
	Mean(Missing)	47.841	37.794	69.864	11.755	18.55255	6.423	.	.
	t	-6.6	-2.6	.4	-5.4	.8	2.6	-1.4	1.0
	df	389.1	379.7	398.4	400.0	490.3	24.7	15.1	3.0
PC.normal	# Present	207	207	202	199	194	16	4	4
	# Missing	610	609	596	607	600	97	15	10
	Mean(Present)	39.710	35.386	84.574	7.598	21.59876	12.031	20.500	10423.000
	Mean(Missing)	46.770	38.089	82.179	11.288	20.21230	7.423	46.333	40.100
	t	-.4	.7	3.0	-.2	.4	2.5	.2	-1.0
	df	98.9	97.5	97.4	103.2	111.2	22.2	13.9	7.0
PC.anxiety	# Present	86	86	86	84	82	18	9	6
	# Missing	731	730	712	722	712	95	10	8
	Mean(Present)	44.360	38.605	116.535	10.179	21.47056	12.778	43.889	52.333
	Mean(Missing)	45.055	37.262	78.709	10.400	20.44516	7.184	38.200	5222.375
	t	5.6	2.8	-1.7	5.3	-1.7	-.1	1.7	-1.0
	df	581.7	559.8	598.3	479.1	458.0	89.3	4.0	10.0
PC.depr	# Present	274	273	268	273	270	47	5	3
	# Missing	543	543	530	533	524	66	14	11
	Mean(Present)	48.774	39.231	75.511	12.875	18.27263	8.000	99.000	89.000
	Mean(Missing)	43.068	36.484	86.463	9.098	21.72506	8.129	20.143	3802.364
	t	-6.0	-3.2	2.6	-5.4	.4	1.6	-1.6	-1.0
	df	50.0	48.9	41.4	61.1	42.8	13.8	12.4	9.0
PC.obses	# Present	38	38	39	39	39	11	6	4
	# Missing	779	778	759	767	755	102	13	10
	Mean(Present)	37.053	33.263	121.615	6.564	22.17949	11.182	18.333	21.500
	Mean(Missing)	45.368	37.605	80.790	10.571	20.46694	7.740	51.308	4200.700
PC.psych	t	.	.	.	.	.	.	.	.

	df	.	.	.	.	.	.	.	.
	# Present	0	0	0	0	0	0	0	0
	# Missing	817	816	798	806	794	113	19	14
	Mean(Present)	.000	.000	.000	.000	.00000	.000	.000	.000
	Mean(Missing)	44.982	37.403	82.785	10.377	20.55106	8.075	40.895	3006.643
Fscopy	t	-1.3	-3.9	-2.8	.3	-1.6	-2.7	-.8	1.0
	df	143.8	139.9	120.2	146.3	112.5	11.9	2.3	10.0
	# Present	705	704	692	697	691	102	16	11
	# Missing	112	112	106	109	103	11	3	3
	Mean(Present)	44.716	36.616	78.238	10.413	19.70122	7.358	34.187	3822.545
	Mean(Missing)	46.652	42.348	112.467	10.147	26.25243	14.727	76.667	15.000
Fscopy.exp	t	.	.	.	.	.	.	.	.
	df	.	.	.	.	.	.	.	.
	# Present	0	0	0	0	0	0	0	0
	# Missing	817	816	798	806	794	113	19	14
	Mean(Present)	.000	.000	.000	.000	.00000	.000	.000	.000
	Mean(Missing)	44.982	37.403	82.785	10.377	20.55106	8.075	40.895	3006.643
Neur.exam	t	.8	-1.2	-2.3	3.2	-1.5	-1.1	-.8	1.0
	df	53.1	52.5	48.0	57.7	41.8	5.5	2.3	10.0
	# Present	769	768	753	759	752	108	16	11
	# Missing	48	48	45	47	42	5	3	3
	Mean(Present)	45.079	37.260	80.786	10.570	19.88037	7.968	34.187	3822.545
	Mean(Missing)	43.417	39.687	116.244	7.255	32.55952	10.400	76.667	15.000
PMT	t	-5.7	-1.4	3.7	-2.3	1.4	3.8	1.0	1.0
	df	509.5	496.3	501.0	538.1	681.7	56.2	16.0	10.0
	# Present	260	260	257	255	256	27	16	11
	# Missing	557	556	541	551	538	86	3	3
	Mean(Present)	40.900	36.408	99.560	9.286	22.19359	12.537	43.563	3821.727
	Mean(Missing)	46.887	37.869	74.816	10.882	19.76948	6.674	26.667	18.000

For each quantitative variable, pairs of groups are formed by indicator variables (present, missing).

a. Indicator variables with less than 5% missing are not displayed.

Appendix B: HydroApp Dashboard snippets

Calculate mean headache duration and pain score (PHP code)

```php
<?php
/**
 * @author Ahmed Al-Jaaf
 * @copyright 2015
 */
include ('../config.php');
$patient_id = $_GET['id'];

if (isset($_GET['start_date']) && isset($_GET['end_date'])) {
        $strat = $_GET['start_date'];
        $end = $_GET['end_date'];
        // query the Table within the requierd start and end dates
        $sql = $mysqli->query("SELECT DISTINCT `headache_date`,
                               `headache_duration`, `pain_score`
                               FROM `headache_diary`
                               WHERE `patient_id` = '$patient_id' AND
                               `headache_date` BETWEEN
                               '$strat' AND '$end'");
} else {
    // return last 20 records reversed,
    // this query will loads by default when dashboard page loads first
       $sql = $mysqli->query("SELECT DISTINCT `headache_date`,
                             `headache_duration`, `pain_score` FROM (
                             SELECT `headache_date`, `headache_duration`,
                             `pain_score` FROM `headache_diary`
                             WHERE `patient_id` = '$patient_id'
                             ORDER BY `headache_date` DESC LIMIT 20) sub
                             ORDER BY `headache_date` ASC");
}
$rowcount=mysqli_num_rows($sql);
     // return how many days patient suffering from
     // headache within a certain time period
if ($rowcount>0) {
        $x=0;
        while ($row = mysqli_fetch_row($sql)) {
                $x++;
                $array_one[] = $row[0]; //  return an array of dates column
                                        // number of headache days
                $array_two[] = $row[1]; // return an array of the second
                                        // column values / duration
                $array_three[] = $row[2]; // return an array of the third
                                        // column values / max_pain
        }
        // start calculation
        $total_duration = 0;
        $total_pain_score = 0;
        for ($i=0; $i<$x; $i++) { // go through the array and
                                  // select the first and last date
                $start_date = $array_one[0]; // Get the start date
                $end_date = $array_one[$x-1]; // Get the last date
                $total_duration += $array_two[$i]; // Get total H. dur.
                $total_pain_score += $array_three[$i]; // Get total P.Sc.
                }
        $temp_duration = $total_duration / $rowcount;
        $temp_score = $total_pain_score / $rowcount;
        $mean_headache_duration = round($temp_duration,2);
        $mean_pain_score = round($temp_score,2);

$jsonData =array (
```

```
    "Start_date" => $start_date,
    "End_date" => $end_date,
    "Headache_days" => $rowcount,
    "Mean_duration" => $mean_headache_duration,
    "Mean_pain_score" => $mean_pain_score
    );
         print json_encode($jsonData);

} else {
    // No query result, empty table or no data for selected time period
$mean_headache_duration = 0;
$mean_pain_score = 0;
$jsonData =array (
    "Start_date" => $strat,
    "End_date" => $end,
    "Headache_days" => $rowcount,
    "Mean_duration" => $mean_headache_duration,
    "Mean_pain_score" => $mean_pain_score
    );
         print json_encode($jsonData);
}
mysqli_close($mysqli); // close the DB connection
?>
```

Visualise headache duration and pain scores (PHP code)

```
<?php
/**
 * @author Ahmed Al-Jaaf
 * @copyright 2015
 */
include ('../config.php');
$patient_id = $_GET['id'];

if (isset($_GET['start_date']) && isset($_GET['end_date'])) {
        $strat = $_GET['start_date'];
        $end = $_GET['end_date'];
        $sql = $mysqli->query("SELECT DISTINCT `headache_date`,
        `headache_duration`, `pain_score`
         FROM `headache_diary`
         WHERE `patient_id` = '$patient_id'
         AND `headache_date` BETWEEN '$strat' AND '$end'");
} else {
    // return last 20 records reversed,
    // this query will loads by default when dashboard page loads first
    $sql = $mysqli->query("SELECT DISTINCT `headache_date`,
    `headache_duration`,
    `pain_score` FROM (
          SELECT `headache_date`, `headache_duration`, `pain_score`
          FROM `headache_diary`
          WHERE `patient_id` = '$patient_id'
          ORDER BY `headache_date` DESC LIMIT 20) sub
          ORDER BY `headache_date` ASC");
}
$result_one['name'] = 'Headache duration / hours';
$result_two['name'] = 'Max pain score / 10';
if($sql->num_rows > 0) {
        while($r = mysqli_fetch_array($sql,MYSQLI_BOTH)) {
            $result_one['category'][] = $r['headache_date'];
            $result_one['data'][] = $r['headache_duration'];
            $result_two['data'][] = $r['pain_score'];
```

```
        }
        $jsonData = array ($result_one,$result_two);
        print json_encode($jsonData, JSON_NUMERIC_CHECK);
}
else{
        $data_one = 0;
        $data_two = 0;
        $result_one['name'] = 'No data available between these two dates';
        $result_two['name'] = 'No data available between these two dates';
            $result_one['category'][] = $strat;
            $result_one['category'][] = $end;
            $result_one['data'][] = $data_one;
            $result_two['data'][] = $data_two;
        $jsonData = array ($result_one,$result_two);
        print json_encode($jsonData, JSON_NUMERIC_CHECK);
}
mysqli_close($mysqli);
?>
```

The Pie chart (JavaScript code)

```
$(document).ready(function() {
        // Mean headache chart - Pie chart
        mean = {
            chart: {
                plotBackgroundColor: null,
                plotBorderWidth: null,
                plotShadow: false,
                renderTo: 'thirdcontainer'
            },
            credits: {
                enabled: false
            },
            title: {
                text: ''
            },
            tooltip: {
                pointFormat: '{series.name}: <b>{point.percentage:.1f}%</b>
'
            },
   plotOptions: {
       pie: {
           //Headache color, Normal color
           colors: ['#EF5350', '#26C6DA'],
           allowPointSelect: true,
           cursor: 'pointer',
           size:'100%',
           dataLabels: {
                enabled: true,
                distance: -30,
                format: '<b>{point.name}</b>: {point.percentage:.1f} %',
                   style: {
                        color: (Highcharts.theme &&
                               Highcharts.theme.contra stTextColor)
                               || 'black'
                    }
                    },
                    showInLegend: true
                }
            },
            series: [{
                type: 'pie',
                name: 'Days',
                data: [],
```

```
                innerSize: '20%'
            }]
        }

// Plotting patients data between a selected dates
    $(function() {
         $('form').submit(function(evt) {
             evt.preventDefault();
             var time = $("#Sdatepicker").val();
             var end = $("#Edatepicker").val();
                if (time != '' && end != '') {

            $.getJSON("includes/php-charts-file/diary.php",
            {id:patient_id, start_date: time, end_date: end},
            function(json){
                  mean.series[0].data = json;
                  chart = new Highcharts.Chart(mean);
            });// end getJSON

       } else {
           alert('Please select a start and end dates that you would like
                  to show results in between. Note that start date should
                  be after the date of setting up a patients account.');
           $("#Sdatepicker").focus();
           }
    }); //end submit function
}); //end function
});// end ready
```

Appendix C: List of publications

1. **A. J. Aljaaf**, D. Al-Jumeily, K. Abdel-Aziz, A. J. Hussain, and M. Al-Jumaily, "M-health Application for Remote Headache Patients Monitoring," *Proc. the 9th Congress of the European Pain Federation (EFIC)*, 2015.
2. **A. J. Aljaaf**, D. Al-Jumeily, A. J. Hussain, T. Dawson, P. Fergus, and M. Al-Jumaily, "Predicting the likelihood of heart failure with a multi level risk assessment using decision tree," *Proc. 2015 Third International Conference on Technological Advances in Electrical, Electronics and Computer Engineering (TAEECE)*, 2015, pp. 101-106.
3. **A. J. Aljaaf**, D. Al-Jumeily, A. J. Hussain, P. Fergus, and M. Al-Jumaily, "WIP16-0232 HEADACHE DIARY: A MOBILE APPLICATION FOR PATIENTS WITH CHRONIC HEADACHE," *Pain Practice*, vol. 16, no. S1, 2016; DOI 10.1111/papr.12451.
4. **A. J. Aljaaf**, D. Al-Jumeily, A. J. Hussain, P. Fergus, M. Al-Jumaily, and K. Abdel-Aziz, "Toward an optimal use of artificial intelligence techniques within a clinical decision support system," *Proc. 2015 Science and Information Conference (SAI)*, 2015, pp. 548-554.
5. **A. J. Aljaaf**, D. Al-Jumeily, A. J. Hussain, P. Fergus, M. Al-Jumaily, and H. Hamdan, "Partially Synthesised Dataset to Improve Prediction Accuracy," *Intelligent Computing Theories and Application: 12th International Conference, ICIC 2016, Lanzhou, China, August 2-5, 2016, Proceedings, Part I*, D.-S. Huang, et al., eds., Springer International Publishing, 2016, pp. 855-866.
6. **A. J. Aljaaf**, D. Al-Jumeily, A. J. Hussain, P. Fergus, and M. Al-Jumaily, "A Systematic Comparison and Evaluation of Supervised Machine Learning Classifiers Using Headache Dataset," *Advanced Intelligent Computing Theories and Applications: 11th International Conference, ICIC 2015, Fuzhou, China, August 20-23, 2015. Proceedings, Part III*, D.-S. Huang and K. Han, eds., Springer International Publishing, 2015, pp. 101-108.
7. **A. J. Aljaaf**, D. Al-Jumeily, A. J. Hussain, P. Fergus, M. Al-Jumaily, and N. Radi, "Applied machine learning classifiers for medical applications:

Clarifying the behavioural patterns using a variety of datasets," *Proc. 2015 International Conference on Systems, Signals and Image Processing (IWSSIP)*, 2015, pp. 228-232.

8. **A. J. Aljaaf**, D. Al-Jumeily, A. J. Hussain, D. Lamb, M. Al-Jumaily, and K. Abdel-Aziz , "A Study of Data Classification and Selection Techniques for Medical Decision Support Systems," *Intelligent Computing Methodologies: 10th International Conference, ICIC 2014, Taiyuan, China, August 3-6, 2014. Proceedings*, D.-S. Huang, et al., eds., Springer International Publishing, 2014, pp. 135-143.
9. **A. J. Aljaaf**, A. J. Hussain, P. Fergus, A. Przybyla, and G. J. Barton , "Evaluation of machine learning methods to predict knee loading from the movement of body segments," *Proc. 2016 International Joint Conference on Neural Networks (IJCNN)*, 2016, pp. 5168-5173.
10. K. Abdel-Aziz, P. Riding, S. Woodham, J. Blanco Rey, S. Maddocks, L. Wainwright, **A. Aljaaf**, D. Al-Jumeily, A. Hussain, M. Al-Jumaily, and P. Fergus, "EHMTI-0276. A novel mobile health application for patients with chronic headache," *The Journal of Headache and Pain*, vol. 15, no. Suppl 1, 2014, pp. D1-D1; DOI 10.1186/1129-2377-15-s1-d1.
11. M. Alloghani, A. Hussain, D. Al-Jumeily, **A. J. Aljaaf**, and J. Mustafina, "Gamification in e-Governance: Development of an Online Gamified System to Enhance Government Entities Services Delivery and Promote Public's Awareness," *Proc. 5th International Conference on Information and Education Technology (ICIET '17)*, ACM, 2017, pp. 176-181.
12. P. Fergus, A. Hussain, J. Hearty, S. Faircloughc, L. Boddya, K. Mackintoshd, G. Strattond, N. Ridgerse, D. Al-Jumeilya, **A. J. Aljaaf**, J. Lunna , "A machine learning approach to measure and monitor physical activity in children," *Neurocomputing*, vol. 228, 2017, pp. 220-230; DOI https://doi.org/10.1016/j.neucom.2016.10.040.

REFERENCES

[1] N. O'Flynn and L. Ridsdale, "Headache in primary care: how important is diagnosis to management?," *The British Journal of General Practice,* vol. 52, pp. 569-573, 2002.

[2] NICE, "Diagnosis and management of headaches in young people and adults," ed, 2012.

[3] IHS, "The International Classification of Headache Disorders, 3rd edition (beta version)," *Cephalalgia,* vol. 33, pp. 629-808, 2013.

[4] SIGN, "Diagnosis and management of headache in adults: A national clinical guideline," ed, 2008.

[5] K. Ravishankar, "The art of history-taking in a headache patient," *Annals of Indian Academy of Neurology,* vol. 15, pp. S7-S14, 2012.

[6] D. Kernick, S. Stapley, and W. Hamilton, "GPs' classification of headache: is primary headache underdiagnosed?," *The British Journal of General Practice,* vol. 58, pp. 102-104, 2008.

[7] M. Morgan, L. Jenkins, and L. Ridsdale, "Patient pressure for referral for headache: a qualitative study of GPs'referral behaviour," *The British Journal of General Practice,* vol. 57, pp. 29-35, 2007.

[8] T. J. Steiner, "Lifting The Burden: The Global Campaign to Reduce the Burden of Headache Worldwide," *The Journal of Headache and Pain,* vol. 6, pp. 373-377, 2005.

[9] T. N. Alliance, "Measuring up: improving the collection of neurological data and intelligence," 2014.

[10] T. Steiner, A. Scher, W. Stewart, K. Kolodner, J. Liberman, and R. Lipton, "The Prevalence and Disability Burden of Adult Migraine in England and their Relationships to Age, Gender and Ethnicity," *Cephalalgia,* vol. 23, pp. 519-527, 2003.

[11] House of Commons, "Headache Disorders - not respected, not resourced: A Report of the All-Party Parliamentary Group on Primary Headache Disorders (APPGPHD)," 2009.

[12] R. Smith, L. A. Hasse, P. N. Ritchey, A. E. Cassedy, and D. J. Rudawsky, "Extent of migraine and migrainous headache in headache NOS patients in family practice," *Cephalalgia,* vol. 21(4), pp. 291-292, 2001 2001.

[13] H. Emsley, "Neurology services in need of new headache pathways to improve productivity," *Health services journal (HSJ),* 2011.

[14] House of Commons, "Headache Services in England: A Report of the All-Party Parliamentary Group on Primary Headache Disorders (APPGPHD)," 2014.

[15] B. Baird, A. Charles, M. Honeyman, D. Maguire, and P. Das, "Understanding pressures in general practice," *King's Fund,* May 2016 2016.

[16] P. J. Goadsby, "To scan or not to scan in headache," *BMJ,* vol. 329, p. 469, 2004.

[17] D. W. Dodick, "Clinical clues and clinical rules: Primary vs secondary headache," *Advanced Studies in Medicine,* vol. 3, pp. S550-S555, Jun 2003 2003.

[18] K. Kennis, D. Kernick, and N. O'Flynn, "Diagnosis and management of headaches in young people and adults: NICE guideline," *The British Journal of General Practice,* vol. 63, pp. 443-445, 2013.
[19] WebMD, "Headache Basics," in *WebMD* vol. 2016, N. S. Lava, Ed., ed. Online: WebMD, 2016.
[20] B. W. Friedman and B. M. Grosberg, "Diagnosis and management of the primary headache disorders in the emergency department setting," *Emergency medicine clinics of North America,* vol. 27, pp. 71-87, viii, 2009/02// 2009.
[21] K. Zafar, Z. Anwar, M. Anwar, W. Ahmed, A. Khan, S. Rehman, and Z. Halim, "Clinical Decision Support System for the Diagnosis of Migraine and Headache," *Journal of Basic and Applied Scientific Research (JBASR),* vol. 3, pp. 119-125, July 2013 2013.
[22] L. RB, B. ME, S. TJ, S. SD, and O. J, "Classification of primary headaches," *Neurology,* vol. 63, pp. 427-435, August 2004 2004.
[23] M. E. Bigal and R. B. Lipton, "Headache classification " in *Migraine and other headache disorders*, R. B. Lipton and M. E. Bigal, Eds., 1st ed: CRC Press, 2006.
[24] F. Ahmed, "Headache disorders: differentiating and managing the common subtypes," *British Journal of Pain,* vol. 6, pp. 124-132, 2012.
[25] S. M, A. C. Lamont, N. A. Alias, and M. N. Win, "Red flags in patients presenting with headache: clinical indications for neuroimaging," *The British Journal of Radiology,* vol. 76, pp. 532-535, 2003/08/01 2003.
[26] BASH, "Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache," ed, 2010.
[27] Z. Katsarava, D. C. Buse, A. N. Manack, and R. B. Lipton, "Defining the Differences Between Episodic Migraine and Chronic Migraine," *Current Pain and Headache Reports,* vol. 16, pp. 86-92, 2012.
[28] D. Buse, A. Manack, D. Serrano, M. Reed, S. Varon, C. Turkel, and R. Lipton, "Headache Impact of Chronic and Episodic Migraine: Results From the American Migraine Prevalence and Prevention Study," *Headache: The Journal of Head and Face Pain,* vol. 52, pp. 3-17, 2012.
[29] S. J. Tepper and D. E. Tepper, "Diagnosis of Migraine and Tension-Type Headaches," in *The Cleveland Clinic Manual of Headache Therapy*, S. J. Tepper and D. E. Tepper, Eds., ed New York, NY: Springer US, 2011, pp. 3-17.
[30] E. Loder and P. Rizzoli, "Tension-type headache," *BMJ,* vol. 336, pp. 88-92, 2008.
[31] L. Arendt-Nielsen, "Headache: muscle tension, trigger points and referred pain," *International Journal of Clinical Practice,* vol. 69, pp. 8–12, 23 April 2015 2015.
[32] G. PJ and L. RB, "A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases," *Brain,* vol. 120, pp. 193-209, 1997 1997.
[33] C. A. Whyte and S. J. Tepper, "Pearls & Oy-sters: Trigeminal autonomic cephalalgias," *Neurology,* vol. 74, pp. e40-e42, March 16, 2010 2010.
[34] M. J. Stillman, "Diagnosis of Trigeminal Autonomic Cephalalgias and Other Primary Headache Disorders," in *The Cleveland Clinic Manual of Headache*

Therapy, S. J. Tepper and D. E. Tepper, Eds., ed New York, NY: Springer US, 2011, pp. 19-36.
[35] IASP, "Trigeminal Autonomic Cephalalgias: Diagnosis and Management," ed, 2012.
[36] T. Sjaastad and I. Dale, "EVIDENCE FOR A NEW (?), TREATABLE HEADACHE ENTITY A PRELIMINARY REPORT," *Headache: The Journal of Head and Face Pain,* vol. 14, pp. 105-108, 1974.
[37] S. Prakash, P. Belani, A. Susvirkar, A. Trivedi, S. Ahuja, and A. Patel, "Paroxysmal hemicrania: a retrospective study of a consecutive series of 22 patients and a critical analysis of the diagnostic criteria," *The Journal of Headache and Pain,* vol. 14, pp. 26-26, 2013.
[38] A. S. Cohen, M. S. Matharu, and P. J. Goadsby, "Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA)—a prospective clinical study of SUNCT and SUNA," *Brain,* vol. 129, pp. 2746-2760, 2006.
[39] L. Bendtsen, S. Evers, M. Linde, D. D. Mitsikostas, G. Sandrini, and J. Schoenen, "EFNS guideline on the treatment of tension-type headache – Report of an EFNS task force," *European Journal of Neurology,* vol. 17, pp. 1318-1325, 2010.
[40] D. C. Buse, A. N. Manack, K. M. Fanning, D. Serrano, M. L. Reed, C. C. Turkel, and R. B. Lipton, "Chronic Migraine Prevalence, Disability, and Sociodemographic Factors: Results From the American Migraine Prevalence and Prevention Study," *Headache: The Journal of Head and Face Pain,* vol. 52, pp. 1456-1470, 2012.
[41] H. L. Rekate, "The definition and classification of hydrocephalus: a personal recommendation to stimulate debate," *Cerebrospinal Fluid Research,* vol. 5, p. 2, January 22 2008.
[42] I. R. Manchester, K. Andersson, J. Malm, and A. Eklund, "System identification for clinical diagnosis of hydrocephalus," in *49th IEEE Conference on Decision and Control (CDC)*, 2010, pp. 3391-3396.
[43] Y. O'Connor, P. O'Reilly, and J. O'Donoghue, "M-health infusion by healthcare practitioners in the national health services (NHS)," *Health Policy and Technology,* vol. 2, pp. 26-35, 2013/03/01/ 2013.
[44] H. M. Chen, Y. Z. Liou, S. Y. Chen, and J. S. Li, "Design of mobile healthcare service with health records format evaluation," in *2013 IEEE International Symposium on Consumer Electronics (ISCE)*, 2013, pp. 257-258.
[45] M. Paschou, E. Sakkopoulos, and A. Tsakalidis, "easyHealthApps: e-Health Apps Dynamic Generation for Smartphones & Tablets," *Journal of Medical Systems,* vol. 37, p. 9951, May 12 2013.
[46] A. A. Al-Hajji, "Rule-Based Expert System for Diagnosis and Symptom of Neurological Disorders Neurologist Expert System (NES)," in *1st Taibah University International Conference on Computing and Information Technology*, Al-Madinah Al-Munawwarah, Saudi Arabia, 2012, pp. 67–72.
[47] R. Hasan, F. Siraj, and S. Hasan, "An Expert System Based Headache Solution," in *2012 IEEE Symposium on Computer Applications and Industrial Electronics (ISCAIE 2012)*, Kinabalu, Malaysia, 2012.
[48] Z. Yin, Z. Dong, S. Yu, X. Lu, G. Feng, and H. Duan, "A Guideline-based Decision Support System for Headache Diagnosis," in *Studies in Health*

Technology and Informatics, C. U. Lehmann, E. Ammenwerth, and C. Nøhr, Eds., ed: IOS Press, 2013.

[49] Z. Dong, Z. Yin, M. He, X. Chen, X. Lv, and S. Yu, "Validation of a guideline-based decision support system for the diagnosis of primary headache disorders based on ICHD-3 beta," *The Journal of Headache and Pain*, vol. 15, pp. 40-40, 2014.

[50] Z. Yin, Z. Dong, X. Lu, S. Yu, X. Chen, and H. Duan, "A clinical decision support system for the diagnosis of probable migraine and probable tension-type headache based on case-based reasoning," *The Journal of Headache and Pain*, vol. 16, p. 29, 2015.

[51] Z. Yin, L. Min, X. Lu, and H. Duan, "A clinical decision support system for primary headache disorder based on hybrid intelligent reasoning," in *2014 7th International Conference on Biomedical Engineering and Informatics*, 2014, pp. 683-687.

[52] B. Krawczyk, D. Simić, S. Simić, and M. Woźniak, "Automatic diagnosis of primary headaches by machine learning methods," *Central European Journal of Medicine*, vol. 8, pp. 157-165, April 01 2013.

[53] S. Simić, D. Simić, P. Slankamenac, and M. Simić-Ivkov, "Computer-Assisted Diagnosis of Primary Headaches," in *Hybrid Artificial Intelligence Systems: Third International Workshop, HAIS 2008, Burgos, Spain, September 24-26, 2008. Proceedings*, E. Corchado, A. Abraham, and W. Pedrycz, Eds., ed Berlin, Heidelberg: Springer Berlin Heidelberg, 2008, pp. 314-321.

[54] S. Simić, D. Simić, P. Slankamenac, and M. Simić-Ivkov, "Rule-Based Fuzzy Logic System for Diagnosing Migraine," presented at the Proceedings of the 5th Hellenic conference on Artificial Intelligence: Theories, Models and Applications, Syros, Greece, 2008.

[55] K. B. Mendes, R. M. Fiuza, and M. T. A. Steiner, "Diagnosis of Headache using Artificial Neural Networks," *IJCSNS International Journal of Computer Science and Network Security*, vol. 10, pp. 172-178, July 2010 2010.

[56] C. Ufuk, Y. Nilufer, K. E. Rabia, T. Nermin, G. Halil, and E. Mustafa, "Migraine, Tension-Type and Cluster-Type of Headaches Classification by Using Immunos Algorithms," *Journal of Medical Imaging and Health Informatics*, vol. 6, pp. 1173-1177, September 2016 2016.

[57] V. Eslami, S. Rouhani-Esfahani, N. Hafezi-Nejad, F. Refaeian, S. Abdi, and M. Togha, "A computerized expert system for diagnosing primary headache based on International Classification of Headache Disorder (ICHD-II)," *SpringerPlus*, vol. 2, p. 199, 2013.

[58] M. Maizels and W. J. Wolfe, "An Expert System for Headache Diagnosis: The Computerized Headache Assessment Tool (CHAT)," *Headache: The Journal of Head and Face Pain*, vol. 48, pp. 72-78, 2008.

[59] K. Zafar, Z. Anwar, M. Anwar, W. Ahmed, A. Khan, S. Rehman, and Z. Halim, "Clinical Decision Support System for the Diagnosis of Migraine and Headache," *Journal of Basic and Applied Scientific Research*, vol. 3, pp. 119-125, July 2013 2013.

[60] A. J. Aljaaf, D. Al-Jumeily, A. J. Hussain, P. Fergus, M. Al-Jumaily, and K. Abdel-Aziz, "Toward an optimal use of artificial intelligence techniques within a clinical decision support system," in *2015 Science and Information Conference (SAI)*, 2015, pp. 548-554.

[61] Y. Y. Chen, K. N. Goh, and K. Chong, "Rule based clinical decision support system for hematological disorder," in *2013 IEEE 4th International Conference on Software Engineering and Service Science*, 2013, pp. 43-48.
[62] A. J. Moses, M. Lieberman, I. Kittay, and J. A. Learreta, "Computer-Aided Diagnoses of Chronic Head Pain: Explanation, Study Data, Implications, and Challenges," *CRANIO®*, vol. 24, pp. 60-66, 2006/01/01 2006.
[63] S. M. Lynch, "Data and Its Acquisition," in *Using Statistics in Social Research: A Concise Approach*, ed New York, NY: Springer New York, 2013, pp. 17-35.
[64] G. Akdal, A. Özge, and G. Ergör, "The prevalence of vestibular symptoms in migraine or tension-type headache," *Journal of Vestibular Research*, vol. 23, pp. 101-106, 2013.
[65] J. Price and D. W. Chamberlayne, "Descriptive and Multivariate Statistics," in *Exploring Crime Analysis: Readings on Essential Skills* S. L. Gwinn, C. W. Bruce, J. P. Cooper, and S. Hick, Eds., 2nd edition ed: BookSurge, 2008, pp. 179-183.
[66] P. Andritsos, "Scalable Clustering of Categorical Data and Applications," Doctor of Philosophy PhD thesis, Department of Computer Science, University of Toronto, Canada, 2004.
[67] C. C. Aggarwal, "Linear Models for Outlier Detection," in *Outlier Analysis*, ed Cham: Springer International Publishing, 2017, pp. 65-110.
[68] J. W. Osborne and A. Overbay, "The power of outliers (and why researchers should ALWAYS check for them)," *Practical Assessment, Research & Evaluation*, vol. 9, pp. 1-8, 2004.
[69] Y. Zhao, "Chapter 7 - Outlier Detection," in *R and Data Mining*, ed: Academic Press, 2013, pp. 63-73.
[70] D. Ghosh and A. Vogt, "Outliers: An Evaluation of Methodologies," in *Section on Survey Research Methods - Joint Statistical Meetings*, 2012, pp. 3455-3460.
[71] C. G. Green and D. Martin, "Diagnosing the Presence of Multivariate Outliers in Fundamental Factor Data using Calibrated Robust Mahalanobis Distances," Department of Statistics, Seattle - WashingtonMay 31, 2015 2015.
[72] G. Dehnel, "Winsorization Methods in Polish Business Survey," *Statistics in Transition - An International Journal of the Polish Statistical Association*, vol. 15, pp. 97-110, 2014.
[73] Z. Zhang, "Missing data imputation: focusing on single imputation," *Annals of Translational Medicine*, vol. 4, p. 9, 2016.
[74] C. T. Tran, M. Zhang, P. Andreae, B. Xue, and L. T. Bui, "Multiple Imputation and Ensemble Learning for Classification with Incomplete Data," in *Intelligent and Evolutionary Systems: The 20th Asia Pacific Symposium, IES 2016, Canberra, Australia, November 2016, Proceedings*, G. Leu, H. K. Singh, and S. Elsayed, Eds., ed Cham: Springer International Publishing, 2017, pp. 401-415.
[75] L. Moyé, "Statistical Methods for Cardiovascular Researchers," *Circulation Research*, vol. 118, pp. 439-453, 2016.
[76] C. T. Tran, P. Andreae, and M. Zhang, "Impact of imputation of missing values on genetic programming based multiple feature construction for classification," in *2015 IEEE Congress on Evolutionary Computation (CEC)*, 2015, pp. 2398-2405.

[77] C. A. Manly and R. S. Wells, "Reporting the Use of Multiple Imputation for Missing Data in Higher Education Research," *Research in Higher Education,* vol. 56, pp. 397-409, 2015.
[78] M. Smuk, "Missing Data Methodology: Sensitivity analysis after multiple imputation," Doctoral, Dept of Medical Statistics, London School of Hygiene & Tropical Medicine, London, 2015.
[79] G. M. Fitzmaurice, M. G. Kenward, G. Molenberghs, G. Verbeke, and A. A. Tsiatis, "Missing Data: Introduction and Statistical Preliminaries," in *Handbook of Missing Data Methodology*, G. Molenberghs, G. Fitzmaurice, M. G. Kenward, A. Tsiatis, and G. Verbeke, Eds., ed: Taylor & Francis Group, 2015.
[80] D. B. Rubin, "Inference and missing data," *Biometrika,* vol. 63, pp. 581-592, 1976.
[81] Y. Dong and C.-Y. J. Peng, "Principled missing data methods for researchers," *SpringerPlus*, vol. 2, p. 222, 2013.
[82] S. v. Buuren, *Flexible Imputation of Missing Data*: Taylor & Francis Group, 2012.
[83] IBM, "IBM SPSS Missing Values 22," USA2013.
[84] C. Y. Peng, M. R. Harwell, S. M. Liou, and L. H. Ehman, "Advances in missing data methods and implications for educational research," in *Real Data Analysis*, S. S. Sawilowsky, Ed., ed New York: Information Age Pub., 2006, pp. 31-78.
[85] J. L. Schafer, "Multiple imputation: a primer," *Statistical Methods in Medical Research,* vol. 8, pp. 3-15, 1999.
[86] D. A. Bennett, "How can I deal with missing data in my study?," *Australian and New Zealand Journal of Public Health*, vol. 25, pp. 464-469, 2001.
[87] B. G. Tabachnick and L. S. Fidell, *Using Multivariate Statistics*. USA: allyn & bacon, 2013.
[88] T. L. Carmack, "A Comparison of Last Observation Carried Forward and Multiple Imputation in a Longitudinal Clinical Trial," Master, Graduate Program in Public Health, The Ohio State University, 2012.
[89] A. Kowarik and M. Templ, "Imputation with the R Package VIM," *2016,* vol. 74, p. 16, 2016-10-20 2016.
[90] T. A. Myers, "Goodbye, Listwise Deletion: Presenting Hot Deck Imputation as an Easy and Effective Tool for Handling Missing Data," *Communication Methods and Measures*, vol. 5, pp. 297-310, 2011/10/01 2011.
[91] A. Y. Kombo, H. Mwambi, and G. Molenberghs, "Multiple imputation for ordinal longitudinal data with monotone missing data patterns," *Journal of Applied Statistics*, vol. 44, pp. 270-287, 2017/01/25 2017.
[92] C. K. Enders, "Multiple imputation as a flexible tool for missing data handling in clinical research," *Behaviour Research and Therapy*.
[93] J. P. Reiter and T. E. Raghunathan, "The Multiple Adaptations of Multiple Imputation," *Journal of the American Statistical Association,* vol. 102, pp. 1462-1471, 2007/12/01 2007.
[94] J. Pallant, *A step by step guide to data analysis using IBM SPSS*: Allen & Unwin, 2013.
[95] A. J. Aljaaf, A. J. Hussain, P. Fergus, A. Przybyla, and G. J. Barton, "Evaluation of machine learning methods to predict knee loading from the movement of body segments," in *2016 International Joint Conference on Neural Networks (IJCNN)*, 2016, pp. 5168-5173.

[96] Z. Mustaffa and Y. Yusof, "a comparison of normalisation techniques in predicting dengue outbreak," in *International conference on business and economics research*, Kuala Lumpur, Malaysia, 2011, pp. 345-349.
[97] T.Jayalakshmi and A.Santhakumaran, "Statistical Normalization and Back Propagation for Classification," *International Journal of Computer Theory and Engineering*, vol. 3, pp. 89-93, 2011.
[98] J. Jin, M. Li, and L. Jin, "Data Normalization to Accelerate Training for Linear Neural Net to Predict Tropical Cyclone Tracks," *Mathematical Problems in Engineering*, vol. 2015, p. 8, 2015.
[99] M. G. Wollsen, J. Hallam, and B. N. Jørgensen, "Novel Automatic Filter-Class Feature Selection for Machine Learning Regression," in *Advances in Big Data: Proceedings of the 2nd INNS Conference on Big Data, October 23-25, 2016, Thessaloniki, Greece*, P. Angelov, Y. Manolopoulos, L. Iliadis, A. Roy, and M. Vellasco, Eds., ed Cham: Springer International Publishing, 2017, pp. 71-80.
[100] J. Silva, A. Aguiar, and F. Silva, "Parallel Asynchronous Strategies for the Execution of Feature Selection Algorithms," *International Journal of Parallel Programming*, pp. 1-32, 2017.
[101] V. Kumar and S. Minz, "Feature Selection: A literature Review," *Smart CR*, vol. 4, pp. 211-229, June 2014 2014.
[102] A. Rehman, K. Javed, and H. A. Babri, "Feature selection based on a normalized difference measure for text classification," *Information Processing & Management*, vol. 53, pp. 473-489, 2017.
[103] S. Nisar and M. Tariq, "Intelligent feature selection using hybrid based feature selection method," in *2016 Sixth International Conference on Innovative Computing Technology (INTECH)*, 2016, pp. 168-172.
[104] L. Ma, M. Li, Y. Gao, T. Chen, X. Ma, and L. Qu, "A Novel Wrapper Approach for Feature Selection in Object-Based Image Classification Using Polygon-Based Cross-Validation," *IEEE Geoscience and Remote Sensing Letters*, vol. 14, pp. 409-413, 2017.
[105] R. Kohavi and G. H. John, "Wrappers for feature subset selection," *Artificial Intelligence*, vol. 97, pp. 273-324, 1997/12/01/ 1997.
[106] L. H. Patil and M. Atique, "A novel feature selection based on information gain using WordNet," in *2013 Science and Information Conference*, 2013, pp. 625-629.
[107] J. Novakovic, "Using Information Gain Attribute Evaluation to Classify Sonar Targets," presented at the 17th Telecommunications forum TELFOR, Serbia, Belgrade, 2009.
[108] D. Wijayasekara, M. Manic, and M. McQueen, "Information gain based dimensionality selection for classifying text documents," in *2013 IEEE Congress on Evolutionary Computation*, 2013, pp. 440-445.
[109] A. M. De Silva and P. H. W. Leong, "Feature Selection," in *Grammar-Based Feature Generation for Time-Series Prediction*, ed Singapore: Springer Singapore, 2015, pp. 13-24.
[110] W. q. Li and X. f. Wang, "Improved Method of Feature Selection Based on Information Gain," in *2012 Spring Congress on Engineering and Technology*, 2012, pp. 1-4.
[111] B.-N. Jiang, X.-Q. Ding, and L.-T. Ma, "A Hybrid Feature Selection Algorithm: Combination of Symmetrical Uncertainty and Genetic

Algorithms," in *The Second International Symposium on Optimization and Systems Biology (OSB'08)*, Lijiang, China, 2008, pp. 152–157.
[112] Y. Yang and Y. Yu, "A hand gestures recognition approach combined attribute bagging with symmetrical uncertainty," in *2012 9th International Conference on Fuzzy Systems and Knowledge Discovery*, 2012, pp. 2551-2554.
[113] B. Singh, N. Kushwaha, and O. P. Vyas, "A Feature Subset Selection Technique for High Dimensional Data Using Symmetric Uncertainty," *Journal of Data Analysis and Information Processing*, vol. 2, pp. 95-105, 2014 2014.
[114] K. J. Ottenbacher, R. T. Linn, P. M. Smith, S. B. Illig, M. Mancuso, and C. V. Granger, "Comparison of logistic regression and neural network analysis applied to predicting living setting after hip fracture," *Annals of Epidemiology*, vol. 14, pp. 551-559, 2004.
[115] J. V. Tu, "Advantages and disadvantages of using artificial neural networks versus logistic regression for predicting medical outcomes," *Journal of Clinical Epidemiology*, vol. 49, pp. 1225-1231, 1996/11/01/ 1996.
[116] S. Agatonovic-Kustrin and R. Beresford, "Basic concepts of artificial neural network (ANN) modeling and its application in pharmaceutical research," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22, pp. 717-727, 2000.
[117] E. Agirre-Basurko, G. Ibarra-Berastegi, and I. Madariaga, "Regression and multilayer perceptron-based models to forecast hourly O3 and NO2 levels in the Bilbao area," *Environmental Modelling & Software*, vol. 21, pp. 430-446, 2006.
[118] H. W. Ressom, R. S. Varghese, Z. Zhang, J. Xuan, and R. Clarke, "Classification algorithms for phenotype prediction in genomics and proteomics," *Frontiers in bioscience : a journal and virtual library*, vol. 13, pp. 691-708, 2008.
[119] M. Paliwal and U. A. Kumar, "Neural networks and statistical techniques: A review of applications," *Expert Systems with Applications*, vol. 36, pp. 2-17, 2009.
[120] F. Souza, T. Matias, and R. Araújo, "Co-evolutionary genetic Multilayer Perceptron for feature selection and model design," in *ETFA2011*, 2011, pp. 1-7.
[121] M. R. Hossain, A. M. T. Oo, and A. B. M. S. Ali, "The Combined Effect of Applying Feature Selection and Parameter Optimization on Machine Learning Techniques for Solar Power Prediction," *American Journal of Energy Research*, vol. 1, pp. 7-16, 2013.
[122] G. Kim, Y. Kim, H. Lim, and H. Kim, "An MLP-based feature subset selection for HIV-1 protease cleavage site analysis," *Artificial Intelligence in Medicine*, vol. 48, pp. 83-89, 2010.
[123] Z. A. Asha'ari, N. Mat Zain, and A. Razali, "Phonophobia and Hyperacusis: Practical Points from a Case Report," *The Malaysian journal of medical sciences : MJMS*, vol. 17, pp. 49-51, Jan-Mar 2010.
[124] D. E. Becker, "Nausea, Vomiting, and Hiccups: A Review of Mechanisms and Treatment," *Anesthesia Progress*, vol. 57, pp. 150-157, Winter 2010.
[125] D. I. Friedman and K. B. Digre, "Headache Medicine Meets Neuro-Ophthalmology: Exam Techniques and Challenging Cases," *Headache*, vol. 53, pp. 703–716, 4 April 2013 2013.

[126] E. Leroux and A. Ducros, "Cluster headache," *Orphanet Journal of Rare Diseases,* vol. 3, p. 20, 2008.
[127] B. Mitchell and R. LeFebvre, "CERVICOGENIC HEADACHE:ASSESSMENT (INCLUDES GENERAL ASSESSMENT OF HEADACHES)," College of Chiropractic, University of Western States, Clinical guidelines13 Jan 2013 2013.
[128] D. P. Turner, T. A. Smitherman, A. K. Black, D. B. Penzien, J. A. H. Porter, K. R. Lofland, and T. T. Houle, "Are Migraine and Tension-Type Headache Diagnostic Types or Points on a Severity Continuum?: An Exploration of the Latent Taxometric Structure of Headache," *Pain,* vol. 156, pp. 1200-1207, 2015.
[129] B. Haque, K. M. Rahman, A. Hoque, A. H. Hasan, R. N. Chowdhury, S. U. Khan, M. B. Alam, M. Habib, and Q. D. Mohammad, "Precipitating and relieving factors of migraine versus tension type headache," *BMC Neurology,* vol. 12, p. 82, 2012.
[130] S. Ashina, L. Bendtsen, A. C. Lyngberg, R. B. Lipton, N. Hajiyeva, and R. Jensen3, "Prevalence of neck pain in migraine and tension-type headache: A population study," *Cephalalgia,* vol. 35, pp. 211–219, 2015.
[131] M. D. Mijajlović, V. M. Aleksić, and N. M. Čovičković Šternić, "Cluster headache as a first manifestation of multiple sclerosis: case report and literature review," *Neuropsychiatric Disease and Treatment,* vol. 10, pp. 2269-2274, 11/25 2014.
[132] S. Benemei, P. Nicoletti, P. Geppetti, and M. Bonciani, "Cataract in chronic cluster headache: two case reports and review of the literature," *The Journal of Headache and Pain,* vol. 9, pp. 401-403, 08/21, 03/10/received, 08/06/accepted 2008.
[133] P. Anttila, L. Metsa¨honkala, M. Mikkelsson, M. Aromaa, H. Kautiainen, J. Salminen, S. Viander, E. Ja¨ppila¨, and M. Sillanpa¨a, "Muscle tenderness in pericranial and neck-shoulder region in children with headache. A controlled study," *Cephalalgia,* vol. 22, pp. 340–344, Jun 2002 2002.
[134] F. Sakai, S. Ebihara, M. Akiyama, and M. Horikawa, "Pericranial muscle hardness in tension-type headache: A non-invasive measurement method and its clinical application," *Brain,* vol. 188, pp. 523-531, April 1995 1995.
[135] G. L. Lipchik, K. A. Holroyd, F. Talbot, and M. Greer, "Pericranial Muscle Tenderness and Exteroceptive Suppression of Temporalis Muscle Activity: A Blind Study of Chronic Tension-Type Headache," *Headache: The Journal of Head and Face Pain,* vol. 37, pp. 368-376, 1997.
[136] A. F. Moraska, L. Stenerson, N. Butryn, J. P. Krutsch, S. J. Schmiege, and J. D. Mann, "Myofascial trigger point-focused head and neck massage for recurrent tension-type headache: A randomized, placebo-controlled clinical trial," *The Clinical journal of pain,* vol. 31, pp. 159-168, 2015.
[137] C. Fernández-de-las-Peñas, C. Alonso-Blanco, M. L. Cuadrado, R. D. Gerwin, and J. A. Pareja, "Myofascial Trigger Points and Their Relationship to Headache Clinical Parameters in Chronic Tension-Type Headache," *Headache: The Journal of Head and Face Pain,* vol. 46, pp. 1264-1272, 2006.
[138] C. Fernández-de-las-Peñas, M. L. Cuadrado, and J. A. Pareja, "Myofascial Trigger Points, Neck Mobility, and Forward Head Posture in Episodic Tension-Type Headache," *Headache: The Journal of Head and Face Pain,* vol. 47, pp. 662-672, 2007.

[139] M. A. Doraisamy, C. p. kumar, Anshul, and C. Gnanamuthu, "Chronic Tension Type Headache and the Impact of Myofascial Trigger Point Release in the Short Term Relief of Headache," *Global Journal of Health Science,* vol. 2, October 2010 2010.
[140] L. J. Stovner and C. Andree, "Prevalence of headache in Europe: a review for the Eurolight project," *The Journal of Headache and Pain,* vol. 11, pp. 289-299, 2010.
[141] Z. Katsarava, A. Dzagnidze, M. Kukava, E. Mirvelashvili, M. Djibuti, M. Janelidze, R. Jensen, L. Stovner, and T. Steiner, "Prevalence of Cluster Headache in the Republic of Georgia: Results of a Population-Based Study and Methodological Considerations," *Cephalalgia,* vol. 29, pp. 949-952, 2009.
[142] T. R. Hoens and N. V. Chawla, "Imbalanced Datasets: From Sampling to Classifiers," in *Imbalanced Learning*, ed: John Wiley & Sons, Inc., 2013, pp. 43-59.
[143] H. He and E. A. Garcia, "Learning from Imbalanced Data," *IEEE Transactions on Knowledge and Data Engineering,* vol. 21, pp. 1263-1284, 2009.
[144] A. Sen, M. M. Islam, K. Murase, and X. Yao, "Binarization With Boosting and Oversampling for Multiclass Classification," *IEEE Transactions on Cybernetics,* vol. 46, pp. 1078-1091, 2016.
[145] M. Aly, "Title," unpublished|.
[146] M. M. Rahman and D. N. Davis, "Addressing the Class Imbalance Problem in Medical Datasets," *International Journal of Machine Learning and Computing,* vol. 3, pp. 224-228, April 2013 2013.
[147] C. Drummond and R. C. Holte, "C4.5, Class Imbalance, and Cost Sensitivity: Why Under-Sampling beats Over-Sampling," 2003 2003.
[148] A. J. Aljaaf, D. Al-Jumeily, A. J. Hussain, P. Fergus, M. Al-Jumaily, and N. Radi, "Applied machine learning classifiers for medical applications: Clarifying the behavioural patterns using a variety of datasets," in *2015 International Conference on Systems, Signals and Image Processing (IWSSIP)*, 2015, pp. 228-232.
[149] A. J. Aljaaf, D. Al-Jumeily, A. J. Hussain, T. Dawson, P. Fergus, and M. Al-Jumaily, "Predicting the likelihood of heart failure with a multi level risk assessment using decision tree," in *2015 Third International Conference on Technological Advances in Electrical, Electronics and Computer Engineering (TAEECE)*, 2015, pp. 101-106.
[150] Scottish Intercollegiate Guidelines Network (SIGN), "Diagnosis and management of headache in adults: A national clinical guideline," Edinburgh, Clinical guideline, November 2008.
[151] J. N. Barlin, Q. Zhou, C. M. St. Clair, A. Iasonos, R. A. Soslow, K. M. Alektiar, M. L. Hensley, M. M. Leitao, R. R. Barakat, and N. R. Abu-Rustum, "Classification and regression tree (CART) analysis of endometrial carcinoma: Seeing the forest for the trees," *Gynecologic Oncology,* vol. 130, pp. 452-456, 2013/09/01/ 2013.
[152] S. Dreiseitl and L. Ohno-Machado, "Logistic regression and artificial neural network classification models: a methodology review," *J. of Biomedical Informatics,* vol. 35, pp. 352-359, 2002.

[153] R. E. Schapire, "Explaining AdaBoost," in *Empirical Inference: Festschrift in Honor of Vladimir N. Vapnik*, B. Schölkopf, Z. Luo, and V. Vovk, Eds., ed Berlin, Heidelberg: Springer Berlin Heidelberg, 2013, pp. 37-52.
[154] UK. government. (2012). *GPs to prescribe apps for patients* [Government]. Available: https://www.gov.uk/government/news/gps-to-prescribe-apps-for-patients
[155] NHS. England. *Enhancing quality of life for people with long-term conditions*. Available: https://www.england.nhs.uk/ourwork/ltc-op-eolc/
[156] RCGR. (2014). *34m patients will fail to get appointment with a GP in 2014*. Available: http://www.rcgp.org.uk/news/2014/february/34-m-patients-will-fail-to-get-appointment-with-a-gp-in-2014.aspx
[157] WHO., "mHealth New horizons for health through mobile technologies," 2001.
[158] D. Mulvaney, B. Woodward, S. Datta, P. Harvey, A. Vyas, O. Farooq, N. Phillip, and R. Istepanian, "Development of m-health monitoring systems in India and Iraq," in *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2012, pp. 288-291.
[159] Oracle, "Siebel REST API Guide," Oracle docs., 2016.
[160] J. F. X. Naradzay, B. J. Browne, M. A. Rolnick, and R. J. Doherty, "Cerebral ventricular shunts11Selected Topics: Critical Care Medicine is coordinated by Joseph Varon, md, of Baylor College of Medicine, Houston, Texas," *The Journal of Emergency Medicine*, vol. 17, pp. 311-322, 1999/03/01/ 1999.
[161] S. R. Browd, B. T. Ragel, O. N. Gottfried, and J. R. W. Kestle, "Failure of Cerebrospinal Fluid Shunts: Part I: Obstruction and Mechanical Failure," *Pediatric Neurology*, vol. 34, pp. 83-92, 2// 2006.
[162] M. Bergsneider, M. R. Egnor, M. Johnston, D. Kranz, J. R. Madsen, J. P. McAllister, C. Stewart, M. L. Walker, and M. A. Williams, "What we don't (but should) know about hydrocephalus," *Journal of Neurosurgery*, vol. 104 PEDIATRICS, pp. 157-159, 2006.
[163] Sagun Tuli, James Drake, Jerry Lawless, Melanie Wigg, and Maria Lamberti-Pasculli, "Risk factors for repeated cerebrospinal shunt failures in pediatric patients with hydrocephalus," *Journal of Neurosurgery*, vol. 92, pp. 31-38, 2000.
[164] K. J. Jeremiah, C. L. Cherry, K. R. Wan, J. A. Toy, R. Wolfe, and R. A. Danks, "Choice of valve type and poor ventricular catheter placement: Modifiable factors associated with ventriculoperitoneal shunt failure," *Journal of Clinical Neuroscience*, vol. 27, pp. 95-98, 5// 2016.
[165] Y. Wu, N. L. Green, M. R. Wrensch, S. Zhao, and N. Gupta, "VENTRICULOPERITONEAL SHUNT COMPLICATIONS IN CALIFORNIA1990 TO 2000," *Neurosurgery*, vol. 61, pp. 557-563, 2007.
[166] R. B. Lipton, S. Diamond, M. Reed, M. L. Diamond, and W. F. Stewart, "Migraine Diagnosis and Treatment: Results From the American Migraine Study II," *Headache: The Journal of Head and Face Pain*, vol. 41, pp. 638-645, 2001.
[167] P. E. Stang and M. V. Korff, "The Diagnosis Of Headache in Primary Care: Factors in the Agreement of Clinical and Standardized Diagnoses," *Headache: The Journal of Head and Face Pain*, vol. 34, pp. 138-142, 1994.