MIXED FEATURES SPECIFIER IN MOOD DISORDER: THE PREVALENCE AND ASSOCIATED FACTORS

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MIXED FEATURES SPECIFIER IN MOOD DISORDER: THE PREVALENCE AND ASSOCIATED FACTORS

ABSTRACT

Introduction: Mixed episode has been an unrelieved source of discussion in the field of psychiatry over the course of two decades as the DSM-IV criteria for both a depressive and manic episode had to be fulfilled to make this diagnosis. Nevertheless, in practice, this threshold was demonstrated to be too high. Therefore, the DSM-5 introduced a less stringent 'specifier' in which three symptoms of the opposite pole suffice thereby creating depression and mania with mixed features, respectively. Literatures points out that approximately 40% of patients have mixed episodes, but this figure may be much higher within the context of DSM-5. Literatures have persistently showed that major mood disorders such as Major Depressive Disorder and Bipolar Disorder with Mixed features are associated with a poorer outcome and a more complex progress of illness.

Methodology: This is a cross sectional prevalence study to determine the prevalence of Mixed Features Specifiers among Major Mood Disorder and its associated factors among outpatient patients. Study was done in Hospital Bahagia Ulu Kinta, Perak using a researcher administered questionnaire which consisted of five parts which includes sociodemographic factors, clinical characteristics, MADRS score, YMRS score and QoL score. All data was analyzed using SPSS version 24.0.

Results: A total of 148 patients were selected as calculated in the sample size calculation for this study. Overall prevalence of MFS among Major Mood Disorder was 29.8%. There were significant associations between ethnicity ($X2=9.063$; df 1; $p=0.028$), marital status ($X2=18.738$; df 1; $p<0.001$) and average monthly income ($X2=31.534$; df 1; $p=<0.001$) with MFS. In terms of clinical characteristics, there were significant associations between number of hospitalizations ($X2=41.026$; df 1; $p<0.001$), trials of medications ($X2=29.540$; df 1; $p<0.001$), total number of medications on ($X2=42.338$; df 1; $p<0.001$), history of ECT ($X2=10.590$; df 1; $p=0.001$), family history of mood disorder ($X2=20.944$; df 1; $p<0.001$), suicidal attempts ($X2=26.570$; df 1; $p<0.001$), history substance use ($X2=19.249$; df 1; $p<0.001$), compliance to treatment ($X2=4.310$; df 1; $p=0.038$), YMRS score ($X2=16.799$; df 1; $p=0.001$) and MADRS score ($X2=43.525$; df 1; $p<0.001$) with MFS. From the results that we obtained, it could identify some associated with MFS which were significant in the sociodemographic factors and clinical characteristics such as amount of income, substance use and number of hospitalizations.

Conclusion: As a conclusion, we fail to reject the alternate hypothesis that there are sociodemographic and clinical characteristics associations with MFS. We also failed to reject the alternate hypothesis that there are significant differences between the QoL of MFS patients and non MFS patients.

Keywords: Mixed Features Specifiers (MFS), Major Mood Disorder, Quality of Life (QoL)

GEJALA BERCAMPUR DIKALANGAN PESAKIT GANGGUAN EMOSI:

KEKERAPAN DAN FAKTOR-FAKTOR BERKAIT RAPAT

ABSTRAK

Pengenalan: 'Mixed Features' atau 'Gejala bercampur' dikalangan pesakit gangguan emosi merupakan satu topik yang hangat diperbincangkan sejak 2 abad yang lalu memandangkan kriteria DSM-IV perlu dipenuhi untuk mendiagnoskan penyakit ini. Namun begitu, kehadiran DSM-V telah memudahkan pakar untuk mengklasifikasikan gangguan emosi beserta gejala bercampur. Kajian menunjukkan bahawa hampir 40% pesakit mempunyai gejala bercampur namun peratusan ini mungkin lebih tinggi jika dikaitkan dengan kriteria DSM-V. Tambahan pula, kajian juga menunjukkan bahawa penyakit beserta gejalai bercampur mempunyai prognosis yang lebih teruk dan perjalanan penyakit yang lebih kompleks.

Methodologi: Ini merupakan satu kajian iris lintang untuk mendapatkan peratusan kekerapan gangguan emosi beserta episode bercampur dikalangan pesakit dan faktor-faktor yang berkait dengannya dikalangan pesakit luar. Kajian ini telah dijalankan di Hospital Bahagia Ulu Kinta, Perak menggunakan borang soal selidik yang terdiri dari 5 bahagian iaitu bahagian sosiodemografik, ciri-ciri klinikal, markah MADRS, markah YMRS dan kualiti hidup (QoL). Semua data dianalisa menggunakan SPSS versi 24.0.

Keputusan: Seramai 148 pesakit ditemu-bual untuk kajian ini. Kekerapan episod bercampur dikalangan pesakit gangguan emosi adalah 29.8%. Antara faktor-faktor yang berkait dengan episode bercampur adalah kumpulan etnik (X2=9.063; df 1; p=0.028), status perkahwinan (X2=18.738; df 1; p<0.001) dan pendapatan bulanan (X2=31.534; df 1; p=<0.001). Bagi ciri-ciri klinikal, yang berkait rapat dengan episod bercampur adalah bilangan kemasukkan wad (X2=41.026; df 1; p<0.001), percubaan perubatan (X2=29.540; df 1; p<0.001), bilangan ubat yang diambil (X2=42.338; df 1; p<0.001), rawatan ECT (X2=10.590; df 1; p=0.001), sejarah keluarga yang menghidapi gannguan mud. (X2=20.944; df 1; p<0.001), percubaan bunuh diri (X2=26.570; df 1; p<0.001), penggunaan bahan larangan (X2=19.249; df 1; p<0.001), pematuhan kepada rawatan (X2=4.310; df 1; p=0.038), markah YMRS (X2=16.799; df 1; p=0.001) dan markah MADRS (X2=43.525; df 1; p<0.001). Daripada keputusan yang diperolehi, terdapat beberapa faktor yang berkait rapat dengan gejala bercampur dikalangan pesakit ganguan emosi.

Kesimpulan: Kesimpulannya, kajian gagal menolak hipotesis alternatif bahawa terdapat faktor-faktor sosiodemografik dan ciri-ciri klinikal yang berkait rapat dengan episode bercampur dikalangan pesakit gangguan emosi. Kajian juga gagal menolak hipotesis alternatif yang menunjukkan perbezaan ketara antara kualiti hidup pesakit '*mixed features'* dan pesakit tanpa '*mixed features'*.

Kata Kunci : Gejala bercampur, gangguan emosi, kualiti hidup

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background

The Concept of mixed states is highly impactful to psychiatry be it historical, conceptual, diagnostic or therapeutic. (McIntyre et al., 2015). Mixed episode has been an unrelieved source of discussion in the field of psychiatry over the course of two decades as the DSM-IV criteria for both a depressive and manic episode had to be fulfilled to make this diagnosis. Nevertheless, in practice, this threshold was demonstrated to be too high. Therefore, the DSM-5 introduced a less stringent 'specifier' in which three symptoms of the opposite pole suffice thereby creating depression and mania with mixed features, respectively. (Malhi et al., 2014). As opposed to previous renditions of the Diagnostic Statistic Manuals, the DSM 5 has adopted the term Mixed features specifier instead of mixed episode.

This enables it to be applied broadly to manic, hypomanic and depressive episodes in both the bipolar spectrum and major depressive disorders. This paradigm shift reflected their significance in the prognosis and overall management of mood disorders, so that the clinicians should thoroughly familiarize themselves with the contemporary notions surrounding these conditions. (Muneer, 2017). Literatures points out that approximately 40% of patients have mixed episodes, but this figure may be much higher within the context of DSM-5. (Shim, Woo, & Bahk, 2015). The wide range of variation.in the reported prevalence of.mixed symptoms and behaviors in Major Depressive Disorder (MDD), Bipolar Disorder (BD) mania/hypomania and BD with Major Depressive

Episodes (MDEs) highlights current imprecision of the 'mixed' episode concept and leaves several uncertainties. (Solé et al., 2017).

The results from Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) shows that manic symptoms, to varying degrees, are present in a substantial number of bipolar I disorder (30%) and bipolar II disorder (71%) patients experiencing a depressive episode. Distractibility, racing thoughts/flight of ideas, and agitation were the most prevalent symptoms. (Goldberg et al., 2009). In patients suffering from Mixed symptoms in depressive phase, the pain of racing thoughts can lead to self- harm such as wrist cutting and drug overdose. Although, racing/crowded thoughts are among the most frequent symptoms in patients with mixed depression, they are rarely reported by patients spontaneously. (Takeshima, 2019).

Compared with non-mixed episodes, mixed manic episodes are characterized by greater mood lability and irritability, and lesser grandiosity, euphoria, need for sleep and pressured speech. The manic symptoms associated with mixed episodes appear to vary in severity, having been reported as less severe, more severe and similar to non-mixed manic episodes. (Swann et al., 2013).

Additionally, several studies also found that considerable manic or mania-related symptoms were admixed during a depressive episode were more frequent amongst the bipolar depressives compared to the unipolar depressive group. (Benazzi, 2000). Evidences points out that mixed features in either Depression and (hypo) mania is linked

with substantial and potentially important differences in clinical and demographic characteristics compared to their counterpart without mixed features. (Tondo et al., 2018).

1.2 Study Rationale

Literatures have persistently showed that major mood disorders such as Major Depressive Disorder and Bipolar Disorder with Mixed features are associated with a poorer outcome and a more complex progress of illness. Additionally, the prevalence rate across various studies varies. To date, there are no studies that examines the prevalence of mixed features in mood disorders among the Malaysian population. A better knowledge on this phenomenon will not only provide early detection among these group of patients, it will also help clinicians understand the complexities of the course. Moreover, a timely and a more appropriate clinical measures could be provided to alter the prognosis of the disease.

1.3 Research Question

The purpose of the study is to answer the following research questions:

- What is the prevalence of Mixed Features Specifiers in Major Depressive Disorder and Bipolar Disorder?
- What is the relationship between Mixed Features Specifiers in Major Depressive Disorder and Bipolar patient with their respective socio-demographic factors?
- What is the relationship between Mixed Features Specifiers in Major Depressive Disorder and Bipolar patient with their severity of symptoms?
- What is the relationship Mixed Features Specifiers in Major Depressive Disorder and Bipolar Disorder and their quality of life?

1.4 Objectives of Study

1.4.1 General Objectives

To study the prevalence of Mixed features specifiers among patients with Major Depressive Disorder and Bipolar Disorder.

1.4.2 Specific Objectives

The specific objectives of this study are as follow:

a) To study the socio demographic characteristics of the patients diagnosed with Mixed features specifiers among patients with Major Depressive Disorder and Bipolar Disorder.
b) To determine the clinical associated factors of patients diagnosed with Mixed features specifiers among patients with Major Depressive Disorder and Bipolar Disorder.
c) To study the QOL of the patients diagnosed with Mixed features specifiers among patients with Major Depressive Disorder and Bipolar Disorder.

1.5 Hypotheses

H1 - There is significant association between socio demographic factors with Mixed Features Specifiers in Major Mood Disorders

H2 - There is significant association between clinical characteristics with Mixed Features Specifiers in Major Mood Disorders

H3 - There is significant differences between QoL and Mixed Features Specifiers in Major Mood Disorders

CHAPTER 2

LITERATURE REVIEW

2.1 Prevalence of Mood Disorders

A study in Canada conducted in 2014 attempted to evaluate the prevalence MFS using the DSM 5 criteria in adults with BD and MDD in a University based Mood Disorder clinic revealed that 33% (n=149) out of 1680 participants met the criteria for mild MFS within the current mood episode. Within these cohort, MFS in hypomanic episode of BD-11 was 5.15(n=8), whereas hypomania without MFS was 0.65%(n=1) while MDE without MFS 62.3%(n=96), MDE with MFS 31.8%(n=49). Among the group of MDD, MDE without MFS was 74% (n=424), where else MDE with MFS was 26% (n=149). The prevalence within the BD-1 is as accordingly; MDE without MFS was 49.4%(n=126), MDE-MFS 25.5%(n=65), mania without MFS 62.3%(n=96), Mania with MFS 19.2%(n=49).

Among the moderately severe group, MDD without MFS was 94.4%(n=541), MDD with MFS 5.6%(n=32), within the BD-1 group, MDE without MFS 63.5%(n=162), MDE with MFS 11.45(n=29), mania without MFS 6.3%(n=16), mania with MFS 16.9% (n=43), hypomania without MFS 1.2%(n=3), hypomania with MFS 0.8%(n=2). The BD-11 group revealed that MDE without MFS 77.3%(n=119), MDE-MFS 16.9%(n=26), Hypomania without MFS 2.6%(n=4), Hypomania with MFS 3.2%(n=5).

Within the severe group of participants, MDD with MFS accounts for 99.8% (n=572), while MDD with MFS was only 0.2% (n=1). The BD1 within the subset of severe clinical presentation showed that, MDE without MFS 74.1% (n=189), MDE with MFS

0.8%(n=2), Mania without MFS 12.2%(n=31), Mania with MFS 11.0% (n=21), hypomania without MFS 1.2%(n=3)0, hypomania with MFS 0.8%(n=2).

Similarly, the prevalence for the BD-11 group were MDE without MFS 94.2%(n=145), MDE-MFS 3.9%(n=6), Hypomania without MFS 1.9%(n=), Hypomania with MFS 0%(n=0).

This study revealed that MFS with regards to MDE was more prevalent with BD-1 and BD-11 compared to the MDD group (χ^2=52.41,df=15,p=0.002) (McIntyre et al., 2015).

However, the limitation within this study was that the participants received a post-hoc diagnosis of MFS rather than an initial diagnosis based on DSM 5. Additionally, the sample was rather limited to compare BD1 to BD-11. This study also did not focus on agitation/ irritability as a criterion for MFS, although many reports highlights a shared occurrence of irritability/ agitation within the Bipolar Spectrum group.(Balázs et al., 2006; McIntyre et al., 2015; Swann et al., 2013)

Conversely, a French study which tried to look at the prevalence of mixed episode of depression within a large sample of MDD group found that among 429 patients only 34% of the subjects had no hypomanic symptoms during their depressive episode (pure depression), while 23.8% had at least three associated hypomanic symptoms. The study also revealed a much lower prevalence of mixed episode when a DSM-IV definition of Mixed episode was used, which is only about 11.2% as compared to a self-assessment with the Multiple Visual Analog Scales of Bipolarity (MVAS-BP) (Azorin et al., 2012).

Correspondingly, an estimate of 25%to 40% of patients with MDD experience simultaneous manic/ hypomanic symptoms during their acute mood episodes. These concurrent symptoms are insufficient to fulfil the criteria for BDI or BDII.

Twenty-five to forty percent of patients with major depressive disorder (MDD) present with concurrent manic symptoms during acute mood episodes that fall short of meeting the criteria for hypomania (bipolar II disorder) or mania (bipolar I disorder).(Akiskal & Benazzi, 2004; Dodd et al., 2010; Goldberg et al., 2009; Miller et al., 2016)

A study in the Asian region namely in Seoul, Korea, investigated the prevalence of Bipolar Disorder with MFS using DSM 5 criteria and compared it with the criteria of DSM –IV TR. This study shows that prevalence mixed episodes were 6.0%, however when using the DSM 5 MFS criteria the prevalence was higher, 15.7% Hypomania/mania with MFS and 3.9% were MDE with MFS. Hence, there were significant difference in the prevalence rate of mixed using the DSM 5 criteria compared to DSM –IV TR ($p<0.001$). However, there are several limitations within this study which are retrospective nature of the diagnoses based on chart review, and treatment emergence mood disorders were not considered (Shim, Woo, & Bahk, 2015).

Similarly, in a multicentre, multinational (BRIDGE-II-MIX) study identified 7.5% of the sample fulfilled MDE-MFS. However, when a wider definition comprising of symptoms which overlaps, the rates rose up to 29.1% (Mcelroy & Keck, 2017).

2.2 Associating Factors and Predictors

2.2.1 Age

There are a wide range of literatures that looked into the sociodemographic factors of mood disorder namely MDD and Bipolar Disorder 1 and 11. Some literatures even compared the sociodemographic data associated with individual specifiers within these disorders.

Among 3099 outpatient group of participants with MDD and BD in Italy, the proportion of mixed episode was 21.9% and the Non mixed was 78.1 %. Amongst this cohort, the mixed showed a younger age of onset as compared with the non-mixed group. (χ^2=6.14, p<0.001). (Tondo et al., 2018).

Concurringly (Shim et al., 2015), Shim et al also found that patients with mixed features had a significantly younger age of onset (21 vs. 34 years; p<0.001). Additionally, they also found that mixed group of subjects had younger age at hospitalization (25 vs. 43 years; p<0.001).

The MDE-MFS cohort was also found to have significantly lower age at first depression and current age. (41.9 ±13.5, p<0.00098). (Brancati et al., 2019).

Interestingly, in a dissimilar study conducted in Italy, which evaluated the demographic and clinical characteristics across various specifiers within MDD, found that, there are statistically insignificant difference between the age of onset of illness of mixed episode, melancholic features and anxious distress (χ^2=3.81, p<0.0225).(Zaninotto et al., 2014).

Therefore, most studies highlights, mixed features present during the mania/ hypomania and depressive episodes a younger age of onset.(Akiskal & Benazzi, 2004; González-Pinto et al., 2007; Hantouche et al., 2006; Lecrubier, 2008; Swann et al., 2013).

Interestingly, in a much recent study that included 12 hospitals in Korea, it was found that although that older age was more prevalent among the unipolar depressive group compared to Bipolar depressive group (p=0.007), the mixed group were younger at the point of recruitment in both the MDD with MFS and MDE with MFS in Bipolar Disorder, however the results were statistically not significant. (p=0.701, 0.587 respectively) (Shim et al., 2019). One of the key limitation of this study was that the sample was among the inpatients only.

2.2.2 Gender

Literature search shows a common evidence that gender differences occur among mixed features groups. A Canadian study which examined the differences of clinical characteristics between the mixed and non-mixed group of both the MDD and BD group revealed that women was somewhat more prevalent compared to men (23.1% vs.19.6%, p=0.02). (Tondo et al., 2018). Similarly, Miller et al pointed out that probability of woman to experience concurrent hypomanic symptoms while suffering from depression is higher (p=0.004) (Miller, Dell'Osso & Ketter, 2014). Contrastingly, a much earlier study in German showed that the gender difference was not significant when compared among the both Unipolar depression with mixed and without mixed state, and Bipolar 1, 11 depressives with or without mixed state (p=0.146). The limitation to this study was that the retrospective identification of hypomanic/manic episodes. (Sato et al., 2003). This findings concurred with a different study conducted within the Asian region, namely Korea in 2015 , found that gender variable between mania/hypomania with MFS and without MFS was not significant (p=0.291) while MDE with MFS and without MFS was akin too (p=0.937) (Shim et al., 2015). This study too, as with the above mentioned study has the limitation of a retrospective nature of diagnosis.

Additionally, this study did not take into account the emergence of mixed mania/hypomania after antidepressants or after electroconvulsive therapy which according to DSM 5, it could be still considered as Bipolar disorder if the symptoms are persistent (Shim et al., 2015). Contrastingly, another study by Shim et al looking at the mixed features among inpatients with both Unipolar depression and Bipolar Depressive episodes in 12 hospitals Korea, found that mixed features were more prevalent in both the group (Shim et al., 2019).

2.2.3 Ethnicity

Psychiatric disorders generally varies across different ethnic groups owing to the genetic predisposition, process of socialization, different load of stresses associated with ethnicity and life adversities.

A Genome–wide association study (GWAS) and Bipolar disorder follow up study which looked at association between the two, found a strong association between genetic variation and Bipolar Disorder (Cichon et al., 2011).

Additionally, dissimilarities in social status between ethnicity and races even within the same geographical location increases the odds of mental illness as well as other adverse social outcomes such as homicide, suicide and substance abuse (Chow, Jaffee, & Snowden, 2003; Wilkinson & Pickett, 2007)

An observation across four national surveys that assessed ethnic and racial differences of mood disorders among Asian, non-Latino Black, Latino and non-Latino Whites between 2001 and 2003 found that non –Latino whites showed a higher prevalence of all disorder types (Mood/ anxiety and substance use disorders) ($p<0.001$) , while Asian , Latino and Black adults have higher prevalence of mood disorders ($p<0.001$).

Among the limitation of this study is that the cross sectional design which limited the authors ability to directly measure the persistence of the disorder. Additional, certain racial groups may have been underrepresented due to smaller representative within the geographical locus (Vilsaint et al., 2019).

In Malaysia, Kader Maideen and colleageus, demonstrated the prevalence of Depressive disorder was highest among other ethnic groups (17.1%) which consist of minorities outside the main 3 ethnics in Malaysia, followed by Chinese (13.8%), Malay (10.8%) and Indian (6.1%). The reporting bias owing to self-report by respondents is one of the main limitations in this study.

A study which attempted to look at prevalence and demographic characteristics between Mixed Features specifiers between both MDD and BD using DSM-5 criteria, found that the racial difference was not statistically significant. However, it is depicted that MFS within the the Depressive episode in BD is relatively higher than non MFS among the African American (6.67% vs 5.52%) and Asian (4% vs 2.07%) and others (5.53% vs 4.83%). Similarly, the MFS within Mania/ hypomania was also higher in Asian (6.98% vs 0%) and other (6.98% vs 0%). Interestingly, within the MDD group, the prevalence of MFS compared to non MFS was only higher among the African American (7.14% vs 5.88%). However, the limitation in this study, was the heterogeneity in the demographics and the small sample size from the minority ethnics (McIntyre et al., 2015).

2.2.4 Education Level

The Cognitive functioning of an euthymic Bipolar patients is not well established as opposed to Schizophrenic patients where the Educational Attainment and lower IQ scores are well documented (Kremen et al., 1995; MacCabe, 2008; Peyrot et al., 2015).

A study published in 2006 which attempted to evaluate the cognitive functioning in BD patients found that Bipolar patients in general completed lesser education level compared to control despite having a comparable IQ(14.1 ± 2 vs. 15.3± 3; F[1, 118]= 5.68, p=0.02). In this study, 16 % of BD patients completed tertiary level of education as compared to the control ($\chi 2$= 18.49, p=0.0001) (Balazs et al., 2006)

The authors further studied the possibility of illness onset affecting the education level and found no difference between the age of onset and education attainment (13.3 ± 2 vs. 14.3 ± 3, respectively; F[1, 58] = 2.62, p= 0.11).

Similarly, the education levels between subgroups of depressive state and manic phase too showed no significant difference ($\chi 2$= 0.18, p= 0.7). Furthermore, the author looked into the possibility of substance abuse as a cause of school drop out, by obtaining a self report from respondents, and interestingly found no differences in level of educational attainment (14.1 ± 2 vs. 14.0 ± 3, respectively; F [1, 58] = 0.07, p= 0.79)

Major Depressive Disorder by itself is also negatively associated with education attainment as observed by Peyrot and colleagues in 2015 when they assessed about 15138 individuals via logistic regression (Peyrot et al., 2015).

2.2.5 Employment status and income

Literature reviews show that Depressive Disorder has a high rates of unemployment status and disability (30.3% to 42.1%) although the employed and unemployed group were similar based on clinical characteristics (Rizvi et al., 2015).

Similarly, BD in general is associated with high rates of job related difficulties and unemployment. About 60% of BD were unemployed and 88% reported job difficulties, although premorbidly, they were degree holders as reported by a survey the National Depressive and Manic-Depressive Association. (Hirschfeld, Lewis, & Vornik, 2003)

When comparing mood disorders with Mixed and without features, Tondo et al found that the mixed features group had a higher unemployment rate compared to the non-mixed group (χ^2=12.9, p=0.0003) (Tondo et al., 2018) . Similar findings were noted in A Canadian study in 2015. This study revealed that within the MDD non MFS, the mean (SD) of employed respondents was 130(44.5), while MDD MFS group was 38 (33.9). Among the BD group, the mean(SD) of employed participants in the group of MDE non MFS was 65 (41.4), the MDE MFS 26 (33.8), hypomania/mania Non MFS 7 (70.0), Hypomania/ mania MFS 20 (44.4) ($p<0.0001$).

There are significant differences in terms of employment status and functionality between the groups without mixed features and with mixed features be it in the MDD or BD patients. It is shown that more individuals with MFS are unemployed or receiving financial aids (X_2=52.41, df=15, adjusted P=0.002).

Additionally, it was reported in the same study that individual within the MDD-MFS group displayed lower workplace productivity as compared to MDD without MFS (Mcintyre, 2017) (Tondo et al., 2018).

2.2.6 Marital status

The relationship between marriage and mental health is complex and possess a wide scope. Marriage could either be stressful life event which could be precipitating factor, predisposing factor or a perpetuating factor in mental illness. On the contrary, there are literatures that highlight marital status as protective factor against mental illness (Dominian, 1979; Hutchinson et al., 1999)

It has also been apparent that individuals with MFS are not married, separated or divorced as compared to their Non MFS counterpart ($p<0.0001$)(Tondo et al., 2018).

Similarly, a Canadian study which attempted to address the prevalence and characteristics of MFS between both MDD in BD found that there are more divorced rates among MFS in MDD (SD =23.2 vs 15.0) and in MFS in BD MDE (SD=18.2 vs 15.3). However, within the BD hypomania/ mania group the divorced rate is lower in the MFS group (SD=8.70 vs 10.0).

Contrastingly, the rate of singlehood was lower among the MDD-MFS and BD MDE-MFS compared to Non-MFS, while, higher in the hypomania/mania-MFS group. Furthermore, this study also assessed the likehood of MFS group to be cohabiting with a partner and found that, across both the disorder regardless of mood states, MFS had a lower preponderance to cohabitate.

Although the findings in this study does not show strong association between marital status owing to the possibility of methodological limitations such as post hoc diagnosis, reporting biases and possible comorbidities, it does signify the importance of marital status as a predictor to the presence of Mixed Feature Specifier (McIntyre et al., 2015).

2.3 CLINICAL CHARACTERISTICS

2.3.1 Family History of mood disorder

Clinicians usually obtain family history routinely, be it for physical or mental illness. Studies has shown there are significant difference between multigenerational family history of mood disorder as compared with single generational family history in terms of illness severity and prognosis of illness. A positive family history of mood disorders showed a positive correlation with a history of abuse in childhood, early age of onset, comorbidity with anxiety and substance abuse, more rapid cycling of mood , multiple episodes, and worsening of severity or frequency of episodes (Antypa & Serretti, 2014; Post et al., 2015). A study which evaluated the characteristic differences between mixed features within the Major Depressive Disorder group and Bipolar Disorder group and with the group without mixed features using the DSM-5 criteria found that mixed cases were more likely to have a family history of Bipolar Disorder (27.8% vs 18.6%,$p<0.0001$). This study also further looked into a family history of suicidal behaviour and a family of any psychiatric illness. It was revealed that the mixed group showed a higher prevalent to both a family history of suicidal behaviour ($\chi^2=5.00$, $p=0.03$) and the latter ($\chi^2=2.75$, $p=0.006$) (Tondo et al., 2018). Contrastingly, a retrospective study conducted by a neighbouring country Korea collecting data from 2003 to 2013 among the Bipolar 1 and 11 Disorder found that the group without mixed features regardless of the episode showed a higher prevalent of family history in general (24.8%vs23.1%, $p=0.747$), a family history of Bipolar Disorder (10.99% vs 4.6%, $p=0.220$), family history of depressive disorder (15.8%vs15.4%, $p=0.751$). These findings were not statistically significant, however there were several limitations when interpreting the results, that the authors declared. Among which was the retrospective data collection and diagnosis based on chart review which could have led to information bias (Shim et al., 2015).

An interesting findings were highlighted by an Italian study that showed mixed episodes had more odds of having a family history of bipolar 11 disorder (OR : 3.4, p=0.000) as compared to a family history of Bipolar 1 disorder (OR 2.4, p=0.136). The family history of Bipolar 11 disorder was higher among the mixed state within the bipolar 11 group as compared to the mixed state of the unipolar depressive group.(p=0.0284) (Akiskal & Benazzi, 2003) . Sato et al replicated this study in a German population and found that mixed features are associated significantly with a family of Bipolar Disorder (χ^2=24.06, p=0.000) while findings of family history of Unipolar Depression (χ^2=0.10, p=0.953), family history of suicide (χ^2=0.04, p=0.850) and family history of substance abuse (χ^2=0.21, p=0.646) were not statistically significant (Sato et al., 2003).

Therefore, there are strong evidences to suggest that mixed features within the mood disorder have a higher association a family history of mood disorder.

2.3.2 The use of combinations of medications

The use of standard antidepressants are widely practiced in the treatment of Major Depressive Disorder. However, the efficacy and safety of these group of drugs among patients with mixed features has neither been fully understood nor established. (Goldberg et al., 2007)

Furthermore, pharmacotherapy for mixed features is challenging because there is a need to treat depressive and manic/ hypomanic symptoms concurrently. There are multiple clinical reports that highlighted the inefficacious outcome for mixed features and association with possible treatment- related complications such as suicidality, agitation, impulsivity and manic switch (Barbuti et al., 2017; Benazzi, 2005; Smith et al., 2009).

Few studies have suggested the use of mood stabilizers and atypical atypical antipsychotic agents as an alternative, there are few clinical trials to support these recommendations.(Faedda et al., 2015; Vieta & Valentí, 2013).

A randomized double blind clinical trial that attempted to evaluate the efficacy of Lurasidone (Atypical Antipsychotic Agent) across different mood states found that there were significantly better response and in remission within the treatment arm compared to the placebo arm (64.8% compared to 30 , $p<0.001$) with a number needed to treat=3. However, one among the several limitations to this study, which are the patients were not enrolled based on DSM 5 criteria for mixed symptoms. (Suppes et al., 2015)

There are varying findings in terms of treatment response towards Lithium (Mood Stabilizer). A study by Freeman et al found that Mixed state was a predictor for poor response towards Lithium. (χ^2= 8.08,p= 0.017) (Sportiche et al., 2017).

Bipolar disorder as an illness is complex and has a high rate of recurrence. Therefore the selection of appropriate medication is crucial for acute management , maintenance treatment and prevention of recurrence. Findings from the Systemic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) conducted from 1998 till 2005 revealed that patients of BD who successfully achieved remission of symptoms were on at least 2.05 medications. Among these medications, Lithium was 37.1% , Valproate was 34.4% and atypical antipsychotic agents were 33.2% (Al Jurdi et al., 2008). Goldberg et al, additionally tried to look at the prevalence of polypharmacy across different mood states within BD and found that 81% from the total sample received complex polypharmacy, among which 53% of the respondent were taking non-psychiatric medications. From these total sample the depressed state receiving complex

polypharmacy was 37%, Manic state 42% while the mixed state were 19%. (Goldberg et al., 2009). Complex polypharmacy in this study was defined as 4 or more medications.

Contrastingly, a prospective study which evaluated the inpatient cohort in 2017 found that the number of medications varied significantly with the subtypes of BD. In bipolar Depression an average of 2.94 medications (SD = 1.19), while in Bipolar Mixed features, 2.69 (SD = 0.97), and 2.40 (SD=0.86) in Bipolar Manic state ($p<0.001$). This study also evaluated the types of medication that is associated with polypharmacy across each mood states. Medications that are highly associated with polypharmacy in the Depressive state were Benzodiazepine (BZ) (OR=11.46), mood stabilizers (MS) (OR = 7.64) and Antidepressant (AD) (OR = 6.69).

Among the Manic state associations were BZ (OR=18.69), SSRI (OR = 9.85), Other AD (OR=7.50), Other AC (OR = 7.23) and SNRI (OR = 5.51). Mixed state evaluation revealed the strongest association of polypharmacy were with Other AD (OR = 8.89), BZ (OR = 5.34) and Other MS (OR = 5.32).

As for BD II, medications most strongly associated with complex polypharmacy were BZ (OR=13.77) and Other MS (OR=6.87). It was further underscored that Lithium had no significant association with complex polypharmacy with depressive state and in mixed state, but has strong association within Manic state and in BD- II.

It was apparent in this study, that complex polypharmacy was significantly associated with re-hospitalization within a short duration. However, the limitation of this study was data are from a single site and the results may not generalize to other settings and patient populations. Furthermore, other confounding factors for rehospitalisation such as medication adherence, symptom severity and changes in prescription upon discharge were not considered.(Golden, Goethe & Woolley, 2017)

2.3.4 Number of hospitalizations

A significant proportion of healthcare use for patients with mood disorder includes hospitalization especially among acute inpatient psychiatric units.(Graca et al., 2013). Furthermore, studies which obtained data from Epidemiological Catchment Area (ECA) in the USA, found that more than half of Bipolar Disorder received some treatment in a year and at least 7% received in patient care (Regier et al., 1993).

A retrospective study of patients with BD and Unipolar Major depression found that BD patient were four times more likely to have been admitted to the hospital over the previous 6 months (Bartels, 2000).

Studies that attempted to look for predictors of health services utilization among mood disorder patients revealed that identical factors associated with poorer outcome amongst mood disorder such as increasing number of episodes, presence of comorbidity, mixed episode and the presence of comorbid substance use had a greater utilization of health care services (Tohen et al., 2003).

A study conducted in Sweden found that , the average length of stay among mixed episodes (42.3 days) were higher compared to pure manic state (29.2 days) or pure depressive state (29.9 days) (Ösby et al., 2009). Similarly , a Spanish study which looked upon a 10-year outcome among the Mixed and non-mixed BD patients found that mixed episode had a higher risk of hospitalization comparatively (OR 2.86, 95% CI, 1.09-7.52,P=0.033) (González-Pinto et al., 2011)

Furthermore, it was found that Mixed episodes is associated frequent emergency department presentation and the need for acute care. This could in turn be associated with the severe psychopathology and the complexity of the episodes (Krüger et al., 2003).

2.3.5 The use of Electroconvulsive Therapy (ECT)

Electroconvulsive therapy (ECT) is widely used for the management of severe and refractory depression. A study conducted by Gruber and his colleagues found that 7 of their medication-resistant mixed state patients had positive outcome upon ECT. The changes in severity was measured using the Schedule for Affective Disorders and Schizophrenia-Change. All the 7 patients were reported to have achieved remission. Therefore, the authors recommended that patients with mixed features who did not respond to initial psychotropic medications should be tried on ECT (Gruber et al., 2000).

Similarly, an Italian study which attempted to compare the response of ECT among patients in Depressed state and mixed state wo are known to be treatment resistant found that there are no significant difference found in the response rate between both the group as measured by Clinical Global Improvement Scale (CGI). However, a significant group effect was present for Young mania total score ($p<0.0001$). However, the difference from baseline to final which was one week after ECT showed good response in both the mixed group and pure depressive group.

However, there were no follow up data that looked into rates relapse after ECT that would suggest a better efficacy of ECT as a treatment option (Medda et al., 2010). These results indirectly suggest that in comparison with Purely depressed bipolar episodes, mixed features are more difficult to treat and may present more residual symptoms.

The lack of the follow-up data was another limitation in this study, and it does not permit to examine the likelihood of relapse as well as the relative need for maintenance medication or continuation of ECT in MS compared with depressive bipolar patients.

Contrastingly, a study conducted among the Indian population, which tried to evaluate the response to ECT across different mood states in Bipolar Disorder found that there are

no significant difference in terms of symptoms improvement among the Depressive state, mixed state and manic state as measured by in Clinical Global Impressions-Severity of Illness scale (CGI-S) scores from pre-ECT to post-ECT. However, this study uses DSM-IV criteria to identify mixed states. Interestingly, the relevant associating factors that was demonstrated in this study was that the Mixed group had a higher trend of ECT and a longer duration of hospital stay as compared to the depressed group. However, the small sample size, lack of blinding , poor randomization were among the glaring limitations in this study (Devanand et al., 2000).

2.3.6 Substance Abuse

Mood disorders namely Depressive disorders and Bipolar disorder commonly co-occur with Substance abuse or Use disorder. Kessler et al in 1997 pointed out the lifetime prevalence rate of any mood disorder was 19.35 and comparatively those with depression were approximately twice more likely and those with bipolar disorder are about seven times more likely to have to have substance use disorder compared to those who do not have these mood disorder. (Kessler et al., 1997)

There are many converging study that shows the association of mood disorders with substance use or abuse. Early literatures have already found earlier age of onset of mood disorder regardless of depressive state or manic state are associated with a higher risk of substance usage. (Christie et al., 1988; Hasin, Endicott, & Lewis, 1985; McGlashan, 1989; Mendlewicz & Baron, 1981). Studies as early as the 1970s has noted the higher association of mixed states with substance use. (Reich, Davies & Himmelhoch, 1974)

A study which attempted to evaluate the differences between manic state and mixed state in 1992, found that there were no significant difference among substance abuse and use disorder between mixed and manic state. (McElroy et al., 1995)

The findings of a much recent study by Cassidy et al who tried to zoom into the patterns of substance use across different subtypes of found that there was no significant difference in the high rates of various substance abuse between pure mania and mixed mania. (Cassidy, Ahearn, & Carroll, 2001).

An American study that assessed the differences between subjects of mixed and non-mixed features which were diagnosed based upon DSM 5 diagnostic criteria in 2018 found that substance use in general was higher among mixed group as compared to the non-mixed group ($p<0.0001$). Tobacco use was 42.6% among Mixed group and 32.7% among the non-mixed group ($p=0.0008$). (Tondo et al., 2018).

In addition to substance use, Mixed features has higher rates of co-occurrence with other psychiatric comorbidity such as ADHD($p=0.03$) and anxiety disorder ($p=0.01$) which is beyond the scope of this study. (Tondo et al., 2018)

These characteristics includes more substance abusers among the mixed features patients, earlier onset of illness and more suicidal ideation and behavior. (Perugi et al., 2015).

The Bridge II Mix study showed that Mixed features were more prevalent among women compared to men. (Perugi et al., 2015). Apart from these differences, it is also highlighted by several studies that, the course of illness is different amongst the mixed group in both the major mood disorder. These groups also has a higher rate of hospitalization, a more prolonged period of illness, and suffers a higher risk of recurrence. (Tondo et al., 2018; Carter et al.,2003)

Another practical observation is that the pharmacotherapy amongst mixed features is challenging because physicians needs to treat both manic/hypomanic and depressive symptoms concurrently (Takeshima, 2019). Literatures points out that Antidepressant usage can exacerbate symptoms of agitation and irritability without improving depressive symptoms. Additionally, the antidepressants may induce a switch to mania or hypomania or ignite an activation syndrome which will in turn lead to newly developed suicidality. (Goldberg et al., 2007; Takeshima, 2019). Studies highlights the mainstay of pharmacological treatment for Mixed features in Depression as Second Generation Antipsychotics. Given the differences in pharmacological strategies for mixed versus non-mixed depression, patients with depression should be assessed for co-existing manic/hypomanic symptoms at each visit, in order to detect mixed depression as early as possible.

Concurrently, subgroups of bipolar disorder with Mixed Features are shown to face greater difficulties in responding to mood stabilizers. (Valentí et al., 2011). Second-generation neuroleptics are emerging as the treatment of choice in the management of mixed states in bipolar disorder (Fagiolini et al., 2015).

2.3.7 Compliance

Adherence or compliance refers to the extent of which an individual corresponds with the health or medical advice or medications provided by the health care provider. It remains a major public health challenge among the non-communicable and communicable diseases (D'Lopez et al., 2006).

Both Major Depressive Disorder and Bipolar Disorder are associated with high rates of poor or non-compliance to medications and follow ups. (Üstün et al., 2004).

DiMatteo and colleagues in 2000 underscored that depressed patients are three times more likely to have poor compliance to treatment compared to the non-depressed with OR 3.03 (95% confidence interval, 1.96-4.89) (DiMatteo, Lepper, & Croghan, 2000).

The findings from the EMBLEM study (The European Mania in Bipolar Longitudinal Evaluation of Medication) across 14 European Countries since 2002, showed that generally both the pure mania and the mixed mania has poor compliance to medications with pure mania being worse than mixed mania at baseline and after at the encounter in the 24th month (Azorin et al., 2009) .

Contrastingly, Bowden et al found that there are premature discontinuation of medications in the mixed manic group which was labelled as dysphoric mania (15.7%) compared to the euphoric mania (7.3%) (p=0.032) as a result medication intolerance. (Bowden, 2005).

2.3.8 Suicidality and Mixed features

Centre for Disease Control and Prevention (CDC) presented a report regarding the leading causes of death in 2017. It was brought to light that suicide that in the United States of America, suicide is the tenth leading causes of death among individuals aged 10 and 34, while among the 35 to 54, suicide is 4th leading cause of death. Interestingly , they have additionally reported that suicide rate is twice more than homicides in United States.(National Institute of Mental Health, 2019; Ishak et al., 2011) .

The term suicidality has a heterogeneous concept involving ideation, parasuicide, serious attempts and completed suicide. According to the National Institute of Mental Health (NIMH), suicide is defined as a death caused by injurious behaviour that is directed to self with an intent to die. While a suicide attempt is a non-fatal potentially injurious

behaviour that is self-directed with an intent to die as a result of the behaviour. Furthermore, it is stated that a suicide attempt may not result in an injury. A suicidal ideation was defined as a process of thought which involves thinking about , planning and considering suicide.(National Institute of Mental Health, 2019).

A survey conducted by the Ministry of Health in Malaysia found that 1288 (6.3%) of 36,519 participants reported of having suicidal ideation (Hayati & Kamarul, 2008). Additionally, our Malaysian National Suicide Registry noted that amongst the completed suicide, Depression was the most common underlying mental illness (Ali et al., 2014; Hayati & Kamarul, 2008)

In fact, MDD among the inpatient was shown to be at a 20-fold risk of a completed suicide and about at least 50% have had at least one suicidal attempt before.

The authors of this study tried to evaluate the correlating factors associated with suicide attempts among the patients with MDD. It was revealed that age 45 and over were significantly less likely than those age 18–29 to have made a suicide attempt (OR = 0.30, 95% CI = 0.17–0.53) and those who were never married were significantly more likely to have a suicidal attempt. (OR = 1.81, 95% CI = 1.08–3.03). An analysis to the individual symptoms pointed out that anhedonia, feeling worthless and excessive guilt as well as the number of depressive symptoms endorsed were also significantly associated with all suicide attempts.(Bolton et al., 2010)

The mixed feature specifier as diagnosed by DSM-5 at the index episode was significantly frequent in patients with suicidal behavior than in patients without suicidal behavior (23.6% vs. 9.0%; P=.001) (Seo et al., 2016). Tondo et al concurred a similar finding and additionally highlighted that individuals with MFS were averagely younger at a first-time suicidal act and reported more suicidal acts and ideation in a lifetime (Tondo et al., 2018).

These findings concurred with much earlier study by Koukopoulos in 1992 pointed out that symptoms presenting as mixed features were associated with suicidal thoughts, attempts which were even impulsive.

Correspondingly, newer articles in accordance with the DSM IV-TR which required meeting both the criteria mania/ hypomania and depression simultaneously also concluded a similar finding. (Swann et al., 2013) Several studies which studied suicidal risk pattern among the MFS group with MDD independently also underscored the higher rates suicidal risk.

MDE + MX cluster presented with significantly shorter duration of current episode, but increased number of previous depressive episodes and lifetime suicide attempts. MDE + MX showed significantly lower age at first depression diagnosis and current age. (Brancati et al., 2019)

2.3.9 Symptom severity

Literature search has not only associated Mixed features in mood disorder with a poorer outcome and complicated course of illness. There are vast literatures that connects Mixed features with a more severe symptomatology as measured across various scales. A study conducted by Miller and colleagues, examined manic and depressive symptoms at each visits of the respondents using Young Mania Rating scale (YMRS) and Inventory of Depressive Symptomatology –Clinician rated version (IDS-C) found that visits mixed depression had a higher YMRS scores for all the items ($p<0.001$). Although each item within the YMRS score had higher yielded in mixed depression compared to pure depression, Irritability (Cohen's d=1.2), language –thought disorder (Cohen'sd=1.1,

Speech rate and amount (Cohen's d=0.9), and increased motor activity and energy (Cohen's d=0.9) were much more prominent in this study. (S. Miller et al., 2016).

Similarly, a study that attempted to assess the illness characteristics of mixed features in both the Major Depressive Disorder and Bipolar Disorder demonstrated that there were no significant difference between hypo/manic episodes of Mixed features and without MFS in terms of YMRS severity. The same study also revealed that the symptoms severity of depressive episodes was higher among the MDD –MFS and Bipolar Depressive phase with MFS using two different scales, Montgomery Asberg Depression Scale (MADRS) mean 35.7, SD:7.6 vs mean 31.5 SD:8.1) and Hamilton Depression Rating Scale-17(HAMD-17) (24.9 SD 5.5, vs 21.8 ,SD 5.8) respectively ($p<0.0001$)(McIntyre et al., 2014).

The Young Mania Rating Scale (YMRS) and Montgomery-Asberg Depression Rating Scale (MADRS) are among the most widely used outcome measures for clinical trials of medications for Bipolar Disorder.

2.4 QUALITY OF LIFE

The World Health Organization defined quality of life as an 'individuals perception of their position in life in terms of their culture , value systems in which they reside in and in relation to their goals, expectations , standards and concerns'.(WHO, 1998).

Literature search reveals numerous definition to QoL, however the term is most often linked to functional impairment or psychosocial functioning. (Greer, Kurian, & Trivedi, 2010).

An analysis to the definition of QoL by WHO, functioning refers to an individual's performance in activities pertaining work , play , relationship as rated by an observer or self, while QoL refers to an individual's satisfaction with one's perception on health and the activities mentioned above (Ishak et al., 2011).

Since the end of the 20th century, QOL has been a key outcome in the planning and evaluation of health services, including the assessment of disease burden and monitoring of treatment effectiveness (Angermeyer, Kilian & Katschnig, 2006; Meijer et al., 2009; Zilcha-Mano et al., 2014)

The proportion of patients with clinically severe impairment (two or more standard deviations below the community norm) in quality of life varied with different diagnoses. This finding is similar across various scales used to measure quality of life.(Cramer, Torgersen & Kringlen, 2010; Jansen et al., 2013; Rapaport et al., 2005).

Cramer et all assessed the QOL across mood disorder on seven aspects including Subjective wellbeing, self-realization, contact with friends, support if ill, negative life events, relation to family of origin, neighbourhood quality ad global quality of life. They found that Non-psychotic major depression is statistically significantly related to all

aspects of QOL while Bipolar Disorder shows less Support if ill than all other mood disorders, and has lower Subjective well-being, more Negative life events, less Contact with family of origin and lower Global quality of life than non-psychotic major depression (Cramer et al., 2010).

Furthermore research has shown that patients with Major Depressive Disorder has poorer QOL compared to patients with physical diseases.(Bonicatto et al., 2001).

It has been evident in various literatures that the Depressive episodes within Bipolar Disorder has a huge impact on the quality of life and functioning of patients (Mazza et al., 2012). Additionally, the presence of mixed mood states has shown to have a huge influence in the illness course and the outcome within Bipolar Disorder as compared to the pure depressive phase.

Votja et al in 2001 found that the self-reported quality of life was significantly lower in mixed states of Bipolar disorder as compared to manic states ($p< 0.001$) where else there are insignificant difference between the depressed states and the mixed states within Bipolar Disorder (Vojta et al., 2001).

A preliminary qualitative study carried out Gitte Lee et al in 2015, pointed out that participants reported that their mixed symptoms were worse than any other state in Bipolar Disorder. Additionally, participants in the same study revealed that important domains within the QoL were most affected during Mixed states. These important domains were distinguished as work, Identity, family life, Relationship , and social life (Mortensen et al., 2015).

There are strong grounds behind the rationale of assessing QoL for Bipolar Disorder. It can be used to evaluate treatment outcomes, treatment adherence and in turn adopt a more

holistic, recovery –oriented assessments (Hope, Page, & Hooke, 2009: Stotland, Mattson, & Bergeson, 2008).

Furthermore, it is apparent that there is incoherence between QoL and symptom change with regards to the response of treatment, whereby symptom changes may lag behind QoL improvement.(Shi et al., 2002).

Interestingly, a one year follow up study that looked at the differences between pure depressive episode and Mixed episode in Bipolar Disorder in Italy found that, Mixed episodes participants experienced faster improvement in terms of social adjustment although they had it worse at the baseline.(Mazza et al., 2012) Additionally, the same study found that there are insignificant difference between the QoL among the pure depressive state and mixed state within Bipolar Disorder.(Mazza et al., 2012).

A study conducted within the Dutch population pointed out that depressive episode shows a statistically significant association with a lower score within the WHOQOL scale as compared to the euthymic and the (hypo)manic group (p=0.05).(Goossens et al., 2008)

A study conducted in Thailand to evaluate the quality of life among Bipolar Disorder patients showed a lower mean value for the domains of physical functioning (75.2±23.9), Role Physical (61.2 ±40.1), Bodily pain (77.6±23.8) , General Health (57.0±22.7). Expectedly, the Role Emotional domain (55.2±42.7) and Mental Health domain (64.6 ±20.1) was also lower compared to the their general population. (Kongsakon et al., 2008).

There are statistically significant differences between the severity of manic features and quality of life shown in a study which evaluated the individual YMRS scores and individual domains of WHOQOL. Patients with a higher YMRS scores showed significant low scores in the social domain of the WHOQOL.(Gazalle et al., 2007).

Correspondingly, there were also statistical significance reported within the Dutch population of Bipolar outpatient group with regards to self-reported psychopathology and the four domains of WHOQOL scales, Physical health (13.93±2.81, p=0.001), Psychological Health (14.17±2.59,p=0.021), Social Relationship (13.99±2.92,p=0.000), reportedly (Goossens et al., 2008).

Association between each item within the YMRS score revealed that item 2 (Increased motor activity- energy) (p=0.005), item 4 (sleep) (p= 0.039), item 5 (Irritability) (p=0.022), had significant impact to the Social Domain of the WHOQOL.

In considering the Physical domain, Item 4(Sleep) (p=0.002), Item 5 (Irritability)(p=0.001) and item 10 (Appearance)(p=0.029) of the YMRS scale shows association with poorer quality of life.

Similarly, Item 4 (Sleep) (p=0.042, 0.004) and 5 (Irritability) (p=0.001) within the YMRS showed significant impairment within the Psychological and Environmental domains of the WHOQOL scale. In addition to this, this study also pointed out that Item 1 (Elevated mood) showed significant positive association to the environmental domain.(Gazalle et al., 2007).

An Iranian study conducted in 2012 evaluated the quality of Bipolar Disorder with a repeated assessment for 1 year points out negative association between WHOQOL-BREF on all the four domains with depression severity as measured by the Hamilton Depression Rating Scale (HDRS) (Sharifi et al., 2012)

Utilizing the linear regression model, it was revealed that the HDRS scores significantly predicted the physical domain (variances 11%-52%), psychological domain (variances, 15-44%), Social domain (variances 13-23%), Environmental domain (variances 8-37%).

A separate analysis of the items within the HDRS scale, pointed out that the Physical domain in the WHOQOL-BREF is negatively associated with the severity of depressed mood ($p<0.01$), higher suicidal impulses ($p<0.01$).

Conceptual Framework

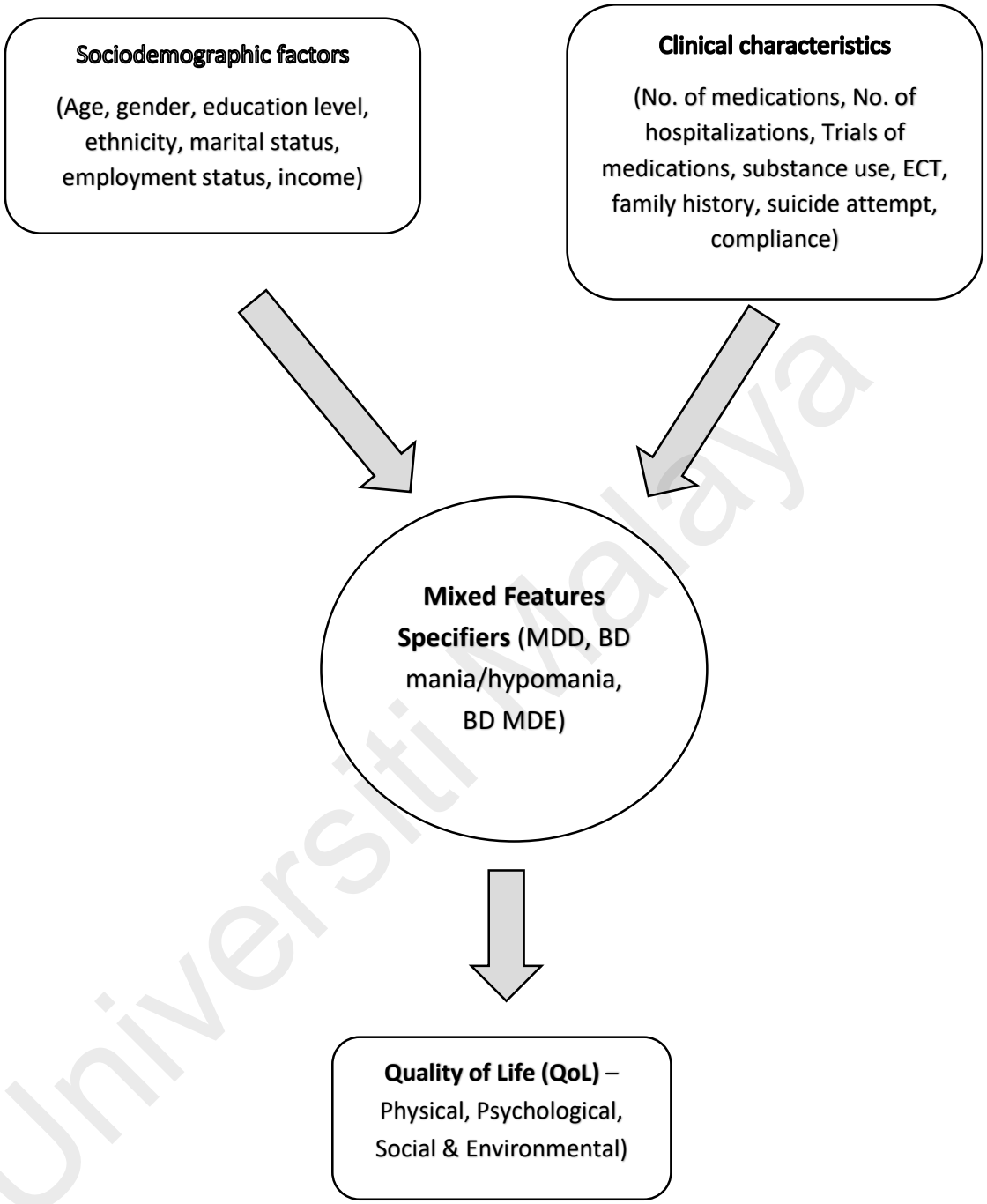

Figure 2.1 Conceptual Framework of study

CHAPTER 3

METHODOLOGY

3.1 Study Location

The study was conducted in Hospital Bahagia Ulu Kinta, which is located 10 km from Ipoh town in Perak. Hospital Bahagia is the oldest mental hospital in Malaysia. It was opened in 1911.

This study will be conducted at Specialist Psychiatric Clinic outpatient setting of Hospital Bahagia Ulu Kinta (HBUK), Tanjung Rambutan, Perak.

The Specialist Psychiatric Clinic in HBUK provides assessment and psychiatric treatment for an average of 1000 outpatient cases every month. The services are provided by the psychiatrist, medical officers, psychologists, counselors with support from the nursing staff. The following treatments are provided:

Psychiatric specialist clinic: The clinic provides consultation by the psychiatrist and medical officer for follow-up cases with prior appointments.

Walk-in clinic: The clinic provides services on work days to new or old cases without appointments. Cases with relapse or crisis are reviewed directly by the medical officer and psychiatrist without later appointment. Most cases would be seen by the walk in clinic prior to admission when received within office hours.

Psychology and counseling: The services are provided for counseling and psychological management.

3.2 Study Design

The study design of this research was a cross-sectional study, which looked at the prevalence of Mixed Feature Specifiers in MDD, BD mania/hypomania and BD MDEs and its associating factors among the respondents who fulfilled the inclusion criteria.

3.3 Study Population

All outpatients in Hospital Bahagia was included as the study population.

3.4 Sampling Population

The sampling population was made up of patients diagnosed with MDD, BD mania/hypomania and BD MDE in Hospital Bahagia Ulu Kinta who visits the outpatient clinic of the hospital during the study period.

3.5 Inclusion and exclusion criteria

Inclusion criteria : 1) Participants who are diagnosed with Major Depressive Disorder or Bipolar disorder using the DSM 5 criteria

2) These participants have provided written informed consent.

3) Participants are within the age range of 18 to 60 years' old

4) Able to converse and comprehend Malay and English language

Exclusion criteria : 1) Individuals with serious medical condition

2) Individuals who has a comorbid of another Major Psychiatric disorder

3) Individuals with severe Intellectual disability

4) Individuals who are too disturbed or disorganized or unable to cooperate

3.6 Sampling Frame

The sampling frame in this study was the list of all patients with the diagnosis of MDD, BD mania/hypomania and BD MDE which was traced from the records department of the hospital.

3.8 Sample Size Estimation

It is unmanageable to inspect each and every one in particular population due to time and financial constraints. Using the following formula from Lemeshow, Hosmer, Klar & Lwanga (1990) and referenced the prevalence to a study done by Miller et al. in 2016 we have obtained the sample size of 148 to be our sample size. Sample size calculation is as shown below:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

n = Sample size

Z = 1.96 (Constant value for 95% confidence)

D = Significance value (0.05)

P = 0.108 (10.8% Expected prevalence from Miller et al., 2016)

Few other calculations were done according to different variables and prevalence value but yielded a far much higher sample size which will affect the feasibility of this study to be performed.

3.9 Sampling method

The sampling method in this study was done using snowball method. All outpatients who was diagnosed as MDD, BD mania/hypomania and BD MDE in the hospital who fulfilled the inclusion criteria was selected for this study. Following that, all patients who visited the outpatient clinic with MDD, BD mania/hypomania and BD MDE who fulfilled the inclusion criteria was taken into this study until sample size was fulfilled.

Participants will be approached by the investigator, after obtaining verbal consent to be seen the by the investigator by the treating doctor during their hospital stay or clinic visits. Participants who has agreed to be seen by the investigator will be given thorough explanation regarding study and be given sufficient time to consider voluntarily on participation in the study. Participants will be able to continue any medications or follow up with their primary treating doctor as usual.

Should the Principal Investigator find that patient condition needs prompt management, the principal Investigator will refer the participant back to the treating doctor.

During the study, the participants will not be provided any form of medications by the principal investigator.

Researcher conducting this study can end the study or end participation at any point of time for the safety of patient, if there is lack of recruitment, decision by the investigator due to safety concerns or inability to sustain or further manage the study. If the study is ended earlier due to certain reason, participants will be informed and treatment will be arranged accordingly after obtaining permission from respondent.

3.10 Study Instrument

Researcher administered the questionnaire to every respondent. The questionnaire consisted of five parts, categorized as A, B, C, D and E described as follows:

Part A - Socio-demographic information (gender, age, ethnicity, marital status, income and education level). A brief questionnaire will be used to obtain all the variables in questionnaires.

Part B – Clinical characteristics. The Diagnostic and Statistical Manual of Mental Disorders (DSM) is the handbook used by health care professionals in the Malaysia and much of the world as the authoritative guide to the diagnosis of mental disorders. DSM contains descriptions, symptoms, and other criteria for diagnosing mental disorders. The latest version is the 5th version. It provides a common language for clinicians to communicate about their patients and establishes consistent and reliable diagnoses that can be used in the research of mental disorders. It also provides a common language for researchers to study the criteria for potential future revisions and to aid in the development of medications and other interventions.

Participants will be directly interviewed using the diagnostic criteria by the clinician within the DSM 5. Patients who fulfils the criteria within the DSM 5 for Major Depressive Disorder and Bipolar Disorder will be further evaluated to fulfil the specifier criteria within DSM 5 to look for Mixed Features Specifier.

Part C – English and Malay version of World Health Organization Quality of Life BREF scale, WHOQOL-BREF. WHOQOL-BREF is a self-administered questionnaire consisting of 26 items that measures quality of life in various populations, on a Likert scale of 1 to 5. Higher scores mean a better quality of life. It is based on the 100-item WHOQOL questionnaires. It aims to improve usability of the original lengthy questionnaire. It measures the impact of disease and impairment on daily activities, behavior and psychological well-being. It consists of two overall items (Overall Quality of Life, and General Health Facet), and 4 domains (Physical Health, Psychological, Social Relationship, Environment).

At the end, it gives six individual scores: scores for the two overall items, and scores for each domain. The domain scores can be transformed into standardized scores ranged from 4 to 20 for comparison across the domains.

In this study, the Malay version of WHOQOL-BREF will be administered. Malay version of WHOQOL-BREF was locally validated by Hasanah et al. (2003). It reported acceptable internal consistency for the four domains (Cronbach's alpha of 0.8 for domain one, 0.62 for domain two. 0.65 for domain three, 0.73 for domain four) and for the whole scale excluded the two overall items (Cronbach's alpha of 0.89). A fair to good test-retest reliability was obtained for each item in the scale, with intra class correlation coefficient range from 0.49-0.88. WHOQOL-Malay is a valid and reliable instrument to be used in Malaysian population.

Permission from the original author will be obtained appropriately before the commencement of the study.

Part D – Young Mania Rating Scale (YMRS). The Young Mania Rating Scale (YMRS), developed by Vincent E Ziegler and popularised by Robert Young, is an eleven-item multiple choice diagnostic questionnaire which are used to measure the presence and severity of mania and associated symptoms.

The YMRS is one of the most frequently utilized rating scales to assess manic symptoms. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours. Concurrent validity of the YMRS with the International Comprehensive Diagnostic Questionnaire was equal to 0.87, and was estimated at 0.89 for the first evaluation and 0.84 for the second evaluation (Young et. al., 2000). Additional information is based upon clinical observations made during the course of the clinical interview. The items are selected based upon published descriptions of the core symptoms of mania. There are four items that are graded on a 0 to 8 scale (irritability, speech, thought content, and disruptive/aggressive behavior), while the remaining seven items are graded on a 0 to 4 scale.

The YMRS baseline scores can vary a lot. They depend on the patients' clinical features such as mania (YMRS = 12), depression (YMRS = 3), or euthymia (YMRS = 2).

Strengths of the YMRS include its brevity, widely accepted use, and ease of administration. The usefulness of the scale is limited in populations with diagnoses other than mania.

Permission from the original author will be obtained appropriately before the commencement of the study.

Part E – MADRS (Montgommery Asberg Depression Rating Scale). It is a ten-item diagnostic questionnaire use to measure the severity of depressive episodes in patients with Mood Disorders. It was designed in 1979 by British and Swedish researcher.

Higher MADRS score indicates more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60.

The questionnaire includes questions on the following symptoms 1. Apparent sadness 2. Reported sadness 3. Inner tension 4. Reduced sleep 5. Reduced appetite 6. Concentration difficulties 7. Lassitude 8. Inability to feel 9. Pessimistic thoughts 10. Suicidal thoughts

Usual cutoff points are:

a) 0 to 6 – normal /symptom absent

b) 7 to 19 – mild depression

c) 20 to 34 – moderate depression

d) >34 – severe depression.

The original English version will be used by the researcher during administration.

Permission from the original author will be obtained appropriately before the commencement of the study.

3.10.1 Diagnosing MFS

In order to diagnosed patients with MFS, DSM 5 criteria was used. In DSM-IV, a diagnosis of mixed episode required an individual to simultaneously meet all criteria for an episode of major depression and an episode of mania. During its review of the latest research, the DSM-5 Mood Disorders Work Group recognized that individuals rarely meet full criteria for both episode types at the same time. In order to be diagnosed with the new specifier in the case of major depression, the new DSM-5 specifier will require the presence of at least three manic/hypomanic symptoms that don't overlap with symptoms of major depression. In the case of mania or hypomania, the specifier will require the presence of at least three symptoms of depression in concert with the episode of mania/hypomania.

3.10.2 Using the Specifiers

If an individual is predominantly manic or hypomanic but also presents with depressive symptoms, the mixed features specifier may be considered. Depressive symptoms may include depressed mood, diminished interest or pleasure, slowed physical and emotional reaction, fatigue or loss of energy, and recurrent thoughts of death. At least three of these symptoms must be present nearly every day during the most recent week of a manic episode or during the most recent four days of a hypomanic episode.

Conversely, if an individual is predominantly depressed with some manic or hypomanic symptoms, the mixed features specifier may also be considered. These manic or hypomanic symptoms may include elevated mood, inflated self-esteem, decreased need for sleep and an increase in energy or goal-directed activity.

At least three of these symptoms must be present nearly every day during the most recent two weeks of the major depressive episode.

All instruments used in this study was validated.

3.11 Variables

3.11.1 Dependent variable

The dependent variable of this study was the:

- Mixed Feature Specifiers (MFS)

3.11.2 Independent variables

The independent variables of this study were the:

- Socio-demographic factors (age, gender, race, marital status, education level, income)
- Clinical Characteristics
- QoL
- YMRS
- MADRS

3.12 Operational Definition

a) Age – Age will be filled up by respondents according to their date of birth. When analyzing using binary logistic regression (BLR), age will be divided into 2 groups.

b) Gender – Gender will be classified as either male or female

c) Ethnicity – Ethnicity will be classified into 4 groups: Malay, Indian, Chinese and Others.

d) Marital status – In binary logistic regression, marital status will be classified into 2 groups: Married or Others (single, divorced, widowed)

e) Education level – Education level will be classified into 2 groups which includes up to secondary or higher than secondary.

f) Average income – average income will be filled by respondents according to their average monthly income and when analyzing using binary logistic regression (BLR), income will be divided into lower (≤1000) and higher (>1000).

g) Employment – Employment is the current status of respondents whether they are employed or not employed.

h) No. of hospitalization – No of hospitalization is the number of admission the respondent has had since diagnosis of mental illness. In binary logistic regression, it is divided into ≤2 and >2.

i) Trials of medications – No of times the medication regime of patients were changed by the treating doctor due to lack of effect.

j) No. of medications – No. of medications are the total number of medications related to mental illness that respondents are on currently. In binary logistic regression, it is divided into ≤2 and >2.

k) History of ECT – History of ECT is whether the patients had any electroconvulsive therapy or not as part of treatment.

l) Family history of mental illness – Family history of mental illness is whether or not respondent has any immediate family members or close relation with mental illnesses.

m) History of suicidal attempts – history of suicidal attempts is whether respondent had attempted suicide before.

n) Substance use – Substance use is whether respondent had history of taking any form of illegal drug in history.

o) Compliance – Compliance is how well patient is taking the treatment prescribed to them accordingly.

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3.13 Ethical Consideration

Prior to research, the researchers obtained approval from the Medical Research & Ethics Committee (MREC) of the Ministry of Health (MOH), Malaysia. An application for ethics approval will be made also to the Research and Ethics Committee, University Malaya Medical Centre. Besides that, application for approval will be obtained from the Ministry of Health and Director of Hospital Bahagia Ulu Kinta. Study subjects will be included on a voluntary basis. The participants will be explained regarding the purpose of the study. Informed consent for participation in the study will be obtained from the subject and a witness before each session. No identifiable information will be collected in this study. The subjects will be allowed to withdraw from the study without having the reasons for withdrawal. This study has no more than minimal risk. No incentives will be given to the participating subjects.

3.14 Privacy and Confidentiality

All data extraction sheets will be coded with the file number instead of patient's name. data extraction sheets will be kept in a locked drawer to ensure confidentiality. For physical study data storage, the study will be kept by hospital authority for ten years and the data will be subjected for audit upon request by relevant authority. The study data will be destroyed after 10 years of data storage.

3.15 Termination of Study

The researcher conducting this study can end the study or end this study at any point of time if it is for participants own safety, if there is lack of recruitment, decision by the investigator due to safety concerns or inability to sustain or further manage the study

3.16 Publication Policy

All the information obtained from this study will be kept confidential and only summarized data will be presented in reports or publications. Permission will be obtained from the Hospital Director if this study will be published later.

The findings or the result of the study will not be informed to subjects.

3.14 Data analysis

Statistical calculations were performed by using the standard statistical software package (SPSS) version 23 for windows. Descriptive statistics including mean, median, standard deviation, frequency and percentage were used to describe both variables. The normality of the data distribution were assessed by normality test using Kolmogorov-Smirnov. All p-values was considered statistically significant at $p<0.05$ at 95% confidence interval (CI). To measure the associations between two categorical variables that will be analyzed using Chi-square test (χ^2), Fisher's exact test was used when more than 20% of cells have expected count of less than 5. The associated factors of MFS were analyzed using multivariate analysis analysis.

CHAPTER 4

RESULTS

4.1 Response Rate

This study was carried out to determine the prevalence of Mixed Feature Specifiers (MFS) in MDD, BD mania/hypomania and BD MDE and its associating factors. In this study, a total of 148 patients were selected as calculated in the sample size calculation.

All respondents were able to answer the necessary questions according to the questionnaire given and guided by the researcher.

The result of this study will be discussed according to the objectives of the study.

4.2 Normality Test

The distribution of data in this study is not normal with both Kolmogrov-Smirnov and Shapiro-Wilk significance level for test of normality is 0.001 and 0.007 respectfully. Thus non parametric test was used to analyze the data in this study.

4.3 Socio-demographic Characteristics of Respondents

The socio-demographic characteristics of respondents can be seen in Table 4.1. The median age of respondents were 34 years old (IQR:32,37). The youngest respondent was 22 years old while the oldest respondent was 46 years old. More than half of respondents were between 30-39 years old (66.2%).

Both male and female genders were almost equally distributed with the percentage of respondents being 50.7% and 49.3% respectively. Majority of respondents (52.0%) were from the Chinese ethnic group.

Majority of respondents were married (85%) while 4.6% were either divorced or widowed.

As for education level, majority of respondents has education level of only up to secondary level (90.5%).

66.9% of respondents were employed. More than half of respondents were earning from <RM1000 monthly (60.8%). This included those who were not employed and not earning any income monthly.

Table 4.1 Socio-demographic distribution of respondents (N=148)

Socio-demographic	n	%
Age Group		
≤30	30	20.3
>30	118	79.7
Gender		
Male	75	50.7
Female	73	49.3
Ethnicity		
Malay	54	36.5
Non Malay	94	63.5
Marital Status		
Single/Divorced/Widowed	46	15.0
Married	261	85.0
Education level		
Up to Secondary	134	90.5
Higher than secondary	14	9.5
Employment		
Employed	99	66.9
Not employed	49	33.1
Average income^		
≤1000	90	60.8
>1000	58	39.2

4.4 Clinical characteristics of respondents

The distribution of respondents according to clinical characteristics is represented in Table 4.2. Majority, 89 (60.1%) of respondents has family history of mood disorder. In terms of number of hospitalization before, 83 (56.1%) had 2 or less hospitalization. Majority (59.5%) of respondents had more than 2 trials of medications. In terms of number of medications respondents are on currently, 64 (43.2%) are on single medication, 57 (38.5%) are on double medications and 27 (18.2%) are on triple medications which includes anti-depressant, anti-psychotics and mood stabilizers. 85 (57.4%) of respondents are on single anti-depressant, 70 (47.3%) are on single anti psychotics and 96 (64.9%) are not on any mood stabilizers. 139 (93.9%) of respondents in this sample did not have any history of ECT, 112 (75.7%) had no history of suicidal attempts before and 107 (72.3%) had no history of substance use previously. 99 (66.9%) of respondents had good compliance to medications and treatment. Most of the respondents had a YMRS score of being in remission – 106 (71.6%). For MADRS scoring, 51 (34.5%) was asymptomatic and 71 (48.0%) had mild depression.

Table 4.2 Distribution of respondents according to clinical characteristics (N=148)

Medical History	n	%
No. of hospitalization		
2 or less	83	56.1
>2	65	43.9
Trials of medication		
2 or less	60	40.5
>2	88	59.5
No. of medication		
Single	64	43.2
Double	57	38.5
Triple	27	18.2
Anti Depressant		
0	55	37.2
1	85	57.4
2	8	5.4
Anti Psychotics		
0	60	40.5
1	70	47.3
2	18	12.2
Mood stabilizers		
0	96	64.9
1	52	35.1
H/O ECT		
Yes	9	6.1
No	139	93.9
Family h/o mood disorder		
Yes	59	39.9

No	89	60.1
History of Suicidal Attempts		
Yes	36	24.3
No	112	75.7
Substance use		
Yes	41	27.7
No	107	72.3
Compliance		
Good	99	66.9
Poor	49	33.1
YMRS		
Remission	106	71.6
Minimal symptoms	36	24.3
Mild mania	3	2.0
Moderate mania	3	2.0
MADRS		
Asymptomatic	51	34.5
Mild depression	71	48.0
Moderate depression	24	16.2
Severe depression	2	1.4

ECT – Electroconvulsive therapy

YMRS – Young Mania Rating Scale (≤12=remission, 13-19=minimal symptoms; 20-25=mild mania, 26-37=moderate mania, 38-60=severe mania))

MADRS - Montgomery–Åsberg Depression Rating Scale (0 to 6–asymptomatic, 7 to 19 – mild depression, 20 to 34–moderate depression, >34 – severe depression)

4.5 Prevalence of MFS among patients with MD

Table 4.3 Prevalence of MFS among MD (N=148)

Classification	Without Mixed Features n (%)	With Mixed Features n (%)
Major Depressive Disorder (MDD)	69 (46.6)	24 (16.2)
Bipolar Disorder (BD) mania/hypomania	20 (13.5)	12 (8.1)
Bipolar Disorder (BD) MDE	15 (10.1)	8 (5.5)
TOTAL	**104 (70.2)**	**44 (29.8)**

MDD – Major Depressive Disorder

MFS – Mixed Features Specifiers

BD – Bipolar Disorder

MDE – Major Depressive Episode

Prevalence of MDD without MFS in this study was 46.6% while MDD with MFS was 16.2%.

Prevalence of BD mania/hypomania without MFS was 13.5% while BD mania/hypomania patients with MFS was 8.1%.

Prevalence of BD MDE without MFS was 10.1% while BD MDE with MFS was 5.5%.

Overall prevalence of MFS among Major Mood Disorder was 29.8%.

4.6 Association between socio-demographic factors with MFS

The association between socio-demographic factors with MFS is shown in Table 4.4. Among the respondents who were diagnosed as MFS, 33.3% were from age group 30 years old or less, 61.6% were females, 38.9% were Malay, 35.7% were either single, divorced or widowed, 35.7% had a higher than secondary level of education, 46.9% were not employed and 46.7% earning on an ≤RM1000 monthly.

There were significant associations between ethnicity (X^2=9.063; df 1; p=0.028), marital status (X^2=18.738; df 1; p<0.001) and average monthly income (X^2=31.534; df 1; p=<0.001) with MFS. Thus, we failed to reject the alternate hypothesis that there are associations between ethnicity, marital status and average monthly income with MFS.

Table 4.4 Association between socio-demographic factors with MFS

Socio demographic	MFS		X^2	df	p
	Yes n (%)	No n (%)			
Age group			0.675	1	0.714
≤30	10 (33.3)	20 (66.7)			
>30	34 (28.8)	84 (71.2)			
Gender			0.543	1	0.073
Male	30 (40.0)	45 (60.0)			
Female	45 (61.6)	33 (38.4)			
Ethnicity			9.063	1	0.028
Malay	21 (38.9)	33 (61.1)			
Non Malay	23 (24.5)	71 (75.5)			

Marital Status			18.738	1	< 0.001
Single/Divorced/Widowed	25 (35.7)	45 (64.3)			
Married	19 (24.4)	59 (75.6)			
Education level			0.265	1	0.607
Up to Secondary	39 (29.1)	95 (70.9)			
Higher than secondary	5 (35.7)	9 (64.3)			
Employment			0.753	1	0.564
Employed	21 (21.2)	78 (78.8)			
Not employed	23 (46.9)	26 (53.1)			
Average income			31.534	1	< 0.001
<1000	42 (46.7)	48 (53.3)			
>1000	2 (3.4)	56 (96.6)			

4.7 Association between clinical characteristics with MFS

The association between clinical characteristics and MFS is shown in Table 4.5. Among the respondents who were with MFS, 56.9% had >2 hospitalizations, 46.6% had >2 trials of medications, 50% are on >2 medications, 77.8% had history of ECT, 50.8% has family history of psychiatric illnesses, 63.9% had history of suicidal attempts, 56.1% had history of substance use and 40.8% had poor compliance to treatment.

There were significant associations between number of hospitalizations (X^2=41.026; df 1; p<0.001), trials of medications (X^2=29.540; df 1; p<0.001), total number of medications on (X^2=42.338; df 1; p<0.001), history of ECT (X^2=10.590; df 1; p=0.001), family history of mood disorder (X^2=20.944; df 1; p<0.001), suicidal attempts (X^2=26.570; df 1; p<0.001), history substance use (X^2=19.249; df 1; p<0.001), compliance to treatment (X^2=4.310; df 1; p=0.038), YMRS score (X^2=16.799; df 1; p=0.001) and MADRS score (X^2=43.525; df 1; p<0.001) with MFS. Thus, we failed to reject the alternate hypothesis that there are associations between medical history with MFS.

Table 4.5 Association between clinical characteristics with MFS

Medical history	**MFS**		**X^2**	**df**	**p**
	Yes n (%)	**No N (%)**			
No. of hospitalization			41.026	1	<0.001
2 or less	7 (8.4)	76 (91.6)			
>2	37 (56.9)	28 (43.1)			
Trials of medication			29.540	1	<0.001
2 or less	3 (5.0)	57 (95.0)			
>2	41 (46.6)	47 (53.4)			
No. of medication			42.338	1	<0.001
2 or less	22 (50.0)	99 (81.8)			
>2	22(50.0)	5 (18.5)			

H/O ECT			10.590	1	0.001
Yes	7 (77.8)	2 (22.2)			
No	37 (26.6)	102 (73.4)			
Family h/o mood disorder			20.944	1	<0.001
Yes	30 (50.8)	29 (49.2)			
No	14 (15.7)	75 (84.3)			
Suicidal Attempts			26.570	1	<0.001
Yes	23 (63.9)	13 (36.1)			
No	21 (18.8)	91 (81.3)			
Substance use			19.249	1	<0.001
Yes	23 (56.1)	18 (43.9)			
No	21 (20.0)	86 (80.0)			
Compliance			4.310	1	0.038
Good	24 (24.2)	75 (75.8)			
Poor	20 (40.8)	29 (59.2)			
YMRS			16.799	3	0.001
Remission	25 (23.6)	81 (76.4)			
Minimal symptoms	13 (36.1)	23 (63.9)			
Mild mania	3 (100)	0 (0)			
Moderate mania	3 (100)	0 (0)			
MDRS			43.525	3	<0.001
Asymptomatic	1 (2.0)	50 (98.0)			
Mild depression	24 (33.8)	47 (66.2)			
Moderate depression	17 (70.8)	7 (29.2)			
Severe depression	2 (100)	0 (0)			

ECT – Electroconvulsive therapy

YMRS – Young Mania Rating Scale (≤12=remission, 13-19=minimal symptoms; 20-25=mild mania, 26-37=moderate mania, 38-60=severe mania))

MADRS - Montgomery–Åsberg Depression Rating Scale (0 to 6–asymptomatic, 7 to 19 – mild depression, 20 to 34–moderate depression, >34 – severe depression)

4.8 Multivariate analysis of MFS (Sociodemographic factors)

Multivariate analysis was used as the analysis method for determining sociodemographic associated factors. 3 sociodemographic variables were included in the preliminary model which are ethnicity, marital status and income as all 3 had significant association using Chi square test. All of the variables were analyzed using 'ENTER', 'Forward-WALD' and 'Backward-WALD'. The 'ENTER' method was selected as it produced the most number of significant associations. There was no collinearity.

MFS patients are 4.1% less likely to be earning an income of >RM1000 (AOR=0.041, 95%CI=0.009-0.181).

Table 4.6 Sociodemographic multivariate analysis of MFS (ENTER Method)

Factors	B	SE	Wald	df	p	AOR	95% CI	
							Lower	Upper
Ethnicity								
Malay						1		
Non Malay	-0.640	0.439	2.119	1	0.145	0.528	0.223	1.248
Marital Status								
Single/Divorced/Widowed						1		
Married	-0.191	0.431	0.197	1	0.657	0.826	0.355	1.922
Income								
≤1000						1		
>1000	-3.188	0.754	17.880	1	<0.001	0.041	0.009	0.181

1 = Reference group

4.9 Multivariate analysis of MFS (Clinical characteristics)

Multivariate analysis was used as the analysis method for determining clinical characteristics associated with MFS. All variables were included in the model as all were significantly associated with MFS.

All of the variables were analyzed using 'ENTER', 'Forward-WALD' and 'Backward-WALD'. The 'ENTER' method was selected as it produced the most number of significant associations. There was no collinearity.

The odds of MFS patients with more than 2 hospitalizations are 18.5 times higher than in patients with less than 2 hospitalizations (AOR=18.487, 95%CI=4.573-74.735).

Patients with MFS are 18.3% less likely to have had no history of substance use if compared with MFS patients (AOR=0.183, 95%CI=0.046-0.726).

Table 4.7 Clinical characteristics multivariate analysis of MFS (ENTER Method)

Factors	B	SE	Wald	df	p	AOR	95% CI	
							Lower	Upper
No of hospitalizations								
≤ 2						1		
> 2	2.917	0.713	16.752	1	<0.001	18.487	4.573	74.735
No of Medications trials								
≤ 2						1		
> 2	21.946	4185.5	0.001	1	0.996	33975	0.001	-
Substance use								
Yes						1		
No	-1.700	0.704	5.831	1	0.016	0.183	0.046	0.726

Suicidal Attempt								
Yes						1		
No	-0.084	0.756	0.012	1	0.911	0.919	0.209	4.047
ECT								
Yes						1		
No	-19.966	4185.46	0.001	1	0.996	0.001	-	-

1 = Reference group

ECT – Electroconvulsive therapy

4.10 Quality of life (QoL) among respondents with MD

In table 4.8, a comparison between the means scores of all 4 domains for QoL between MDD and MDD MFS is presented. Mann-Whitney U test was performed to see the differences between mean scores and results shows that all 4 domains has significant differences between the mean scores in respondents with MDD and respondents with MDD MFS.

Table 4.8 QoL differences between MD with MFS and non MFS

Domain	Group, Mean (SD)		Test	Value	p-value
	MDD	**MDD MFS**			
Physical	62.32 (7.518)	48.04 (6.147)	*U*	9.229	<0.001
Social	61.54 (8.010)	50.54 (8.251)	*U*	5.665	<0.001
Psychological	59.20 (8.588)	36.67 (9.379)	*U*	10.357	<0.001
Environmental	60.55 (9.995)	46.50 (3.022)	*U*	10.392	<0.001

MDD – Major Depressive Disorder

MFS – Mixed Features Specifiers

In table 4.9, a comparison between the means scores of all 4 domains for QoL between BD mania/hypomania and BD mania/hypomania. Mann-Whitney U test was performed to see the differences between mean scores and results shows that all 4 domains has significant differences between the mean scores in respondents with BD mania/hypomania and respondents with BD mania/hypomania MFS.

Table 4.9 QoL differences between BD mania/hypomania with MFS and non MFS

Domain	Group, Mean (SD)		Test	Value	p-value
	BPD mania/hypo	BPD mania/hypo MFS			
Physical	56.00 (10.285)	48.00 (4.671)	*U*	3.001	0.006
Social	55.25 (10.109)	47.50 (4.758)	*U*	2.930	0.007
Psychological	45.25 (14.980)	29.58 (5.435)	*U*	4.235	<0.001
Environmental	52.10 (9.994)	45.50 (4.523)	*U*	2.550	0.016

BD – Bipolar Disorder

MFS – Mixed Features Specifiers

In table 4.10, a comparison between the means scores of all 4 domains for QoL between BD MDE and BD MDE MFS is presented. Mann-Whitney U test was performed to see the differences between mean scores and results shows that all 4 domains has significant differences between the mean scores in respondents with BD MDE and BD MDE MFS.

Table 4.10 QoL differences between BPD II with MFS and non MFS

Domain	Group, Mean (SD)		Test	Value	p-value
	BD MDE	BD MDE MFS			
Physical	62.27 (7.035)	47.00 (3.207)	*U*	7.129	<0.001
Social	62.27 (7.787)	46.25 (3.105)	*U*	6.992	<0.001
Psychological	52.07 (11.823)	32.75 (7.421)	*U*	4.799	<0.001
Environmental	63.93 (7.304)	45.50 (5.318)	*U*	6.922	<0.001

BD – Bipolar Disorder

MDE – Major Depressive Disorder

MFS – Mixed Features Specifiers

CHAPTER 5

DISCUSSION

5.1 Prevalence of MFS

The existence of concurrent manic and depressive symptoms in a single nosology is recognized as mixed states and has been recognized since the time of Emil Kraeplin (Pacchiarotti et al., 2013). Its definition and dimension has faced a dynamic evolution process over time as its presence and significance has become more apparent (Goldberg, Perlis, et al., 2009). In the DSM-IV and DSM –IVTR, the diagnosis of mixed symptoms requires the presence of both the diagnostic criteria of depression and hypo/mania simultaneously (American Psychiatric Association, 2013). This stringent diagnostic requirement has led to the emergence of the new DSM ~~5~~ criteria which is believed to be less stringent. Therefore, DSM-5 acknowledges the presence of mixed symptoms by calling it Mixed Feature Specifier and enables the diagnosis of MFS across Major Depressive Disorder, Bipolar 1 Disorder and Bipolar II Disorder.

The usage of different criteria in identifying mixed features has yielded varying prevalence values as evidenced by the abundant studies found in today's literature~~s~~. It is postulated that the prevalence rate of Mixed Feature Specifier using the DSM ~~5~~ V criteria should be much higher compared to the DSM IV-TR due to the less stringent criteria requirement (Giuli Perugi et al., 2015).

In this study, among the 148 respondents that were recruited, the prevalence of MDD MFS among MDD patients is 16.2%. The prevalence rate shown in this study is much greater than a study conducted by Shim and colleagues which only found about 6.5% of

all its Major Depressive Episode patients with mixed features. Both the studies used DSM 5 criteria.

However, the sample population and methodology varied whereby Shim and colleagues focused on an inpatient sample and a retrospective history obtained from chart review. The possibility of reviewer bias could have been present as no structured interviews were conducted. Furthermore, certain symptoms such as racing thoughts could have been missed during routine clinical review of patients. Additionally, when a diagnosis of mixed features was made according to a broader research based criteria (RCBC), a much higher prevalence was obtained (31 -61.8%) (Shim et al., 2019).

In the context Bipolar Disorder, this study demonstrated the prevalence of MFS among BD mania/hypomania patients is 8.1%, while the prevalence of MFS among BD MDE patients is 34.8%. The overall prevalence rate of Bipolar patients diagnosed with mixed features across the literature is approximately 40%, beginning from the 1970s up to the present time. (Fagiolini et al., 2015; Himmelhoch et al., 1976; Kessing, 2008).

The prevalence rate of MFS across both mood states in Bipolar Disorder in this study, corresponds to the prevalence obtained by McIntyre and colleagues within the Canadian population. It was found that 39.4% of patients in MDE had MFS while 37.8% of patients with hypo/mania had MFS (McIntyre et al., 2015).

Although, the prevalence rates are relatively similar overall, there are some discrepancies identified in the study conducted in HBUK which had a lower prevalence rate of MFS within the MDD group. The variation in the results could be contributed by several factors. This study has a relatively smaller number of patients among the Bipolar group. In addition, the sampled population consisted of outpatients, leading to the exclusion of patients with more severe symptomatology. Furthermore, this is a cross-sectional study

that looked into the current mood episode and did not take into account the history of previous mood states.

Moreover, this study was conducted during the period of the Movement Control Order (MCO) that the country adopted in response to the Covid-19 pandemic (National Security Council, 2020). This resulted in limited number of patients visiting the clinic as HBUK adopted the policy of teleconsultation and mobile medication dispensing. According to McIntyre at al, the highest prevalence of MFS among the Bipolar Disorder group lies in the mild to moderate severity range (R S McIntyre et al., 2013) Hence, in line with this finding, there was a likelihood that patients with mild severity may not have attended clinic review and hence not recruited in this study.

Many studies across the globe have underscored the high prevalence of the younger age category within the MFS group (Benazzi, 2007; Fagiolini et al., 2015; Pacchiarotti et al., 2013; Shim et al., 2015). However, the sociodemographic characteristics within the catchment area in this study has a higher preponderance towards the older age group which could contribute to the divergence in the results obtained in this study (Department of Statistics Malaysia, 2020). The age factor could be further influenced by the MCO, as the younger age group were more likely to be working out of the catchment area and were prevented from traveling back to their regular hospitals for follow-up.

This study was conducted by a single researcher, hence there is a high likelihood of researcher bias in terms of obtaining data pertaining to the prevalence of MFS which may have led to the discrepant findings compared to the other studies. The small number of patients within this study made it impossible to assess the prevalence of MFS among Bipolar II Disorder subgroup.

Although the present study has several limitations in recognizing the prevalence that could be generalized, data when taken together alongside with comparable evidences in other studies, found that there is a relatively high prevalence rate of MFS among mood disorders.

This study hence provides an indirect inference that mixed features specifier remains underdiagnosed as the symptoms overlaps and are subjective, requiring detailed clinical assessment. A report produced by Takeshima demonstrated that racing thoughts, irritability and psychomotor agitation are commonly present among MDD with MFS (Takeshima, 2019).

Therefore, this study may aid in future research as well as clinical practice since MFS is associated with a poorer prognosis in mood disorders.

5.2 Sociodemographic factors of MFS

5.2.1 Age

The median age of respondents in this study was 34 years old (IQR:32,37). The youngest respondent was 22 years old while the oldest respondent was 46 years old. More than half of respondents were between 30-39 years old (66.2%). Among the respondents who were diagnosed as MFS, 33.3% were from age group 30 years old or less. Both, Tondo et al and Shims and colleagues found that patients with Mixed features have a younger age of onset. Shim additionally found that this group also had a younger age at first hospitalization. (Shim et al., 2015; Vázquez et al., 2018). Most of the age group among studies carried out globally in various regions point to an average age of onset of less than 34 years old (Brancati et al., 2019; Jansen et al., 2013; Shim et al., 2019; Tondo et al., 2018).

Although, the findings in this study is similar to most studies, the results were not significant. This study concurred with a more recent finding in another Asian country, that showed that a younger age of onset was not significant in mixed features. The key limitation in this study was that the sample was only among the inpatient group (Shim et al., 2019). The statistically insignificant findings in this study could be attributed to the general demographics in this hospital where most of the residents within this geographical locus belong to an older population. Additionally, during the point of sample collection, Malaysia was undergoing a movement control disorder which restricted interstate movement. Hence most of the working class patients could have been missed. Nevertheless, a younger age of onset translates to a longer disease burden and a longer duration of life lived with disability. By acknowledging this, thorough screening of symptoms must be performed to enable an appropriate treatment plan to be conjured in order to reduce the adverse outcomes associated with the Mixed Features Specifier.

5.2.2 Gender

In this study, both male and female genders were almost equally distributed with the percentage of respondents being 50.7% and 49.3% respectively. Among the respondents who were diagnosed as MFS, 61.6% were females. Studies have shown that women are more likely to suffer from mood disorders namely depressive disorders (Jansen et al., 2013; Miller et al., 2014; Waraich et al., 2004)

Studies carried out in Malaysia to evaluate the prevalence of depression in various settings such primary care and in the general community also noted similar findings. (Maideen et al., 2015; Mukhtar & Oei, 2011; Varma & Azhar, 1995).

Conversely, an interesting study conducted by Ahmad and colleagues within the clinical setting found that more males suffer from mood disorders when they have an underlying medical comorbidity (Tin, 2002).

In this study, the similar distribution of respondents could be explained by the demographic distribution within the proximity of Hospital Bahagia.

Tondo and his colleagues found that women are more likely to experience mixed episodes compared to males.(Vázquez et al., 2018). A German study was able to distinguish that women reported a higher prevalence of mixed symptoms during the depressive phase. (Miller et al., 2014).

Although within this sample population, female were more likely to experience mixed symptoms, the findings were not statistically significant, similar to the findings by Sato and colleague.(Sato et al., 2003)

The findings by Sato and colleagues could be attributed to the retrospective nature of diagnosis that was carried out in the study. This could have led to information bias. While, the results obtained in this study could have been obscured by the equal distribution of gender among the respondents in the sample population.

Furthermore, women tend to be more adherent to medications and follow-ups.(Hadji, Jacob, & Kostev, 2016; Sundbom & Bingefors, 2012). Therefore, the insignificant association of women in this study could have been explained by women achieving euthymia or greater improvement in symptoms.

Some studies found that women experiences mixed symptoms more in depressive states compared to manic or hypomanic states. (Sato et al., 2003). This study did not look into mixed symptoms in separate disorders but grouped as a whole. Therefore, further studies are warranted to evaluate the effect of gender on Mixed Feature Specifier within Major Depressive Disorder and Bipolar Disorder.

Mood Disorders, independently, have already been associated with a poorer quality of life and and impaired functioning. The presence of mixed symptoms further contributes to this adverse outcome.

Hence, it is prudent to note that gender is an important predictor for mixed depression.

5.2.3 Ethnicity

In this study, majority of respondents (52.0%) were from the Chinese ethnic group. Although the majority constituents of Malaysia are the Malay ethinicity, the majority ethnic distribution within the proximity of HBUK are Chinese and the least are the Indian Ethnic. This study corresponds with few local studies that showed a higher prevalence of

Mood Disorders namely depressive disorders among the Chinese ethnicity (Maideen et al., 2015; Zuraida & Ahmad, 2007).

The sample from both these studies were in Klang Valley and Selangor. Although based on the statistics of ethnic distribution presented by the Department of Statistics of Malaysia, the majority ethnicity in Selangor are Malays, however, the socioeconomic status, the ethnic density around within the catchment area may have contributed to the findings.

Contrastingly, in another local study which aimed to identify the prevalence rate of Bipolar Disorders among mothers attending the Postnatal Clinic in University Malaya Medical Centre (UMMC) found a higher prevalence of Bipolar Spectrum disorder among the Malay ethnicity, followed by the Chinese and Indians (Ng et al., 2009)).

In this study, it was discovered that, there is a significant association of Mixed feature specifier among the Malays (38.9%), ($X2=9.063$; df 1; $p=0.028$). This result could be by explained the greater tendency of ~~the~~ Chinese patients to seek ~~for~~ private psychiatric consultation and treatement compared to the Malays. Furthermore, the lower education level, and lower socioeconomic status among the Malays could explain the higher symptom severity, which have led to the findings in this study. Additionally, this study was conducted during the Movement Control (MCO) which was strictly practised nationwide in response to the spread of Covid-19 pandemic, where the visits of patient to the clinic was reserved for more severe cases, and the number patients that visited the clinics were also limited. This could have contributed to demographic variation among the other local studies and statistics presented by the National Health Morbidity Survey (Yeoh et al., 2017). Furthermore, during the MCO period, most patients who are working in a different district or state, were not allowed to travel interstate. According to National

Department of Statistics, the labour force participation is the highest among the Chinese ethnic. Furthermore, the unemployment rate among the Malay ethnic was demonstrated to be much higher than the Chinese ethinc in the country (Aun, 2020). Therefore, the small sample size and methodological limitation could have contributed to the higher prevalence of MFS within the Malay ethnic.

According to established evidence, the mixed feature specifier is strongly associated with other comorbidities such as substance use and Attention Deficit Hyperactivity Disorder, which could also lead to higher health resources utilization rate which was not considered in this study. In line with the report published by The National Anti-Drug Agency

(AADK), the incidence of substance abuse if higher among the Malays (72%), followed by the Chinese (17.8%) and Indians (5.2%).(Mahmood Nazar et al., 2008).

There are no previous studies done locally to look at the prevalence of mixed feature specifier, hence the findings in this study that showed a strong association of ethnicity with MFS should provide an opportunity for future studies to look into this aspect. A study that assessed the importance of religious coping in suicide and mood disorders showed that the Muslim religion which is the fundamental religion among the Malays, is a salient protective factor (Zuraida & Ahmad, 2007). This could aid in providing a better outcome and prognosis among the Mixed Feature Specifier subgroup.

5.2.4 Marital status

Majority of respondents in this study were married (85%) while 4.6% were either divorced or widowed. Among the respondents who were diagnosed as MFS, 35.7% were either single, divorced or widowed. There were significant associations between marital status ($X2=18.738$; df 1; $p<0.001$) with MFS. The findings in this study concurs with

similar studies conducted globally that showed the higher likelihood of MFS to be either single, separated, or divorced (McIntyre et al., 2015; Tondo et al., 2018).

However, unlike those studies, this study did not look into the likelihood of marital status in different mood states across Bipolar Disorder and MDD.

Mood Disorders have also been strongly associated with sexual dysfunction which could be consequent to pharmacotherapy that the patient is on or due to the severity of depressive symptoms itself. (Clayton & Montejo, 2006; Ferguson, 2001; Rothmore, 2020) Sexual dysfunction is an important predictor to marital discord and divorce as it causes severe psychological distress to the patient and also the spouse.(Balon, 2017) Mixed features, in addition to the complex symptomatology is associated with polypharmacy which increases the vulnerability to sexual side effects and reduced libido. However, this was not evaluated in this study.

Among the symptoms within manic and mixed state is hyper sexuality. Kopeykina and colleagues examined the quality of couple relationship among Bipolar Disorder patients and found that there is reduced levels of sexual satisfaction associated with hyper sexuality, unstable levels of sexual interest in different mood states and increased incidence of sexual dysfunction in this group of patients, adding to the strain in romantic relationships between couples.(Kopeykina et al., 2016).

Other possible factors that could also contribute to the higher prevalence of single/ separated or divorce status among patients are presence of legal issues, financial constraints and impaired social and occupational functioning.(Clayton & Montejo, 2006; Kendurkar & Kaur, 2008; Lam et al., 2005; Nehra et al., 2014)

As pointed in this study and many other studies, Mixed feature specifier has strong associations with other predictors of divorce and separation, hence further leading to poorer social support and quality of life.

5.2.5 Education Level

As for education level, majority of the respondents have an education level of only up to secondary level (90.5%). Among the respondents who were diagnosed as MFS, 35.7% had a higher than secondary level of education. The general education level among the respondents in this study corresponds to low educational attainment as demonstrated by several other articles.(Erickson et al., 2016; Glahn et al., 2006; Mezuk et al., 2008)

In this study, the association of education level was not statistically significant when compared with patients without mood disorder.

Additionally, the average education level among the residents within the proximity of HBUK is up to secondary school which could also negatively affect the findings in this study. Furthermore, other factors such as comorbid of substance abuse, financial constraints, logistic reasons, which could also lead to increase incidences of school drop outs are not controlled for in the studies.

5.2.6 Employment status and Income

Mood Disorders and employment status have been studied rather extensively worldwide. Mood disorders has been highly associated with increased rates of job-related difficulties and unemployment. In fact, a survey conducted by the Depressive and Manic-Depressive Association, revealed that about 60% of this group of patients are unemployed while

about 90% of them suffered from job related difficulties (Kupfer, Frank, Grochocinski, Houck, & Brown, 2005). In this study however, the majority of the respondents were employed as opposed to the findings of most studies.(Mcintyre, 2017; Rizvi et al., 2015; Vázquez et al., 2018).

However, this result corresponds to a previous local study Taha and Colleagues which found about 59.7% of patients with depressive disorder were employed in a full time job , while 4.1% of them were affiliated with a part time job.(Taha et al., 2005)

In our study, however, we did not segregate the employment status as part time or full time. Additionally, the difference in the results could be attributed to the sample population which is from the outpatient cohort where most symptoms are remitted. Additionally, the study by Taha and colleagues too was focused upon patients attending primary care services in peninsular Malaysia where patients are more stable, or are attending clinics for maintenance therapy. (Taha et al., 2005)

In terms of income, more than half of the respondents were earning less than RM1000 monthly (60.8%). This included those who were not employed and not earning any income. According to the Minimum Wages Order 2020, that was gazetted in the beginning of January 2020, the minimum monthly wage was fixed at RM 1200 for employees whose place of employment is within the City and Municipal Councils, while the rest was set at RM 1100. This recent increment was set to aid the rising cost of living within the country as well as to boost the cost of production. Nonetheless, the findings in this study indicate that the average income is far below than the standards of the minimal wage even in relatively well patients. (Wage, 2020).

Therefore, it could be inferred that although most the respondents are working, there is low financial stability.

The analysis of employment status among patients with MFS in this study found that a higher proportion (46.9%) are unemployed even if employed are earning less than RM 1000 monthly. There were significant associations between average monthly income (X2=31.534; df 1; p=<0.001) with MFS. In terms of sociodemographic predictors of this study, MFS patients are 4.1% less likely to be earning an income of >RM1000 (AOR=0.041, 95%CI=0.009-0.181).

This results concords with the findings of Tondo and McIntyre which showed significant associations too.(Roger S. McIntyre et al., 2015; Pacchiarotti et al., 2013; Vázquez et al., 2018). Furthermore, as opposed to this study, McIntyre and colleagues further scrutinized the unemployment rate within MFS across both MDD and BD and in both the polarity. It was found that, MDD-MFS, MDE-MFS had a higher unemployment rate compared to MFS within the hypo/mania group.(Roger S. McIntyre et al., 2015)

This study however, did not look into the employment status across both the polarity. Furthermore, the significant association unemployment rate and low wage identified in this study could contribute to the high financial aid provided by the Jabatan Kebajikan Masyarakat (JKM) Malaysia. The rate of financial assistance provided by JKM increases annually and amounting to RM 1,528,600.6 in 2015.as reported by Jabatan Kebajikan Masyarakat in 2015. Although, the constituent of financial aid for the category of mental illness in the same report was 8% from the allocated fund, it should be born in mind that the requirement in other aspects of the fund such as medical comorbidity, physical disability, funding for child care, education fund, involvement in substance and purchasing of medical devices are not included and is highly related to a patient with mental illness.(Jabatan Kebajikan Masyarakat, 2014)

Hence, this association is prudent and should be evaluated thoroughly in future researches, as employment status affects not only the quality of life of patients, family members of patients, the illness progression but also implicates strongly on the global economic burden of the country.

5.3 Clinical characteristics of MFS

5.3.1 Familial history of mood disorder

Majority, 89 (60.1%) of respondents has family history of mood disorder. Among the respondents who were with MFS, 50.8% has family history of Mood Disorder. Similar to other studies, this study shows a significant positive correlation between a family history of mood disorder. (Akiskal & Benazzi, 2003; Antypa & Serretti, 2014; Shim et al., 2015; Tondo et al., 2018). This study however did not determine the type of mood disorder that was present in the family history as depicted by Tondo and his colleagues which showed MFS has a significant correlation with a family history of Bipolar Disorder. However, the findings in a neighboring country, Korea showed in the retrospective cohort study, that MFS regardless of the episode showed a correlation with both types of Mood Disorder. (Shim et al., 2015). Additionally, similar studies which looked further into suicidal family history among MFS, showed significant association between them.(Tondo et al., 2018). Similarly , a large population database study revealed that parental diagnosis of Bipolar Disorder and parental depression with psychosis are important predictors for the switch incidences from unipolar depression to Bipolar Disorder.(Musliner & Østergaard, 2018)

Therefore, it is evident that family history of mood disorders is a significant predictor for mixed features specifier in both Major Depressive Disorder and Bipolar Disorder. This should raise as a red flag sign during clinical practice in identifying potential risk factors for MFS.

5.3.2 Number of hospitalizations

In terms of number of previous hospitalization before, 83 (56.1%) had 2 or less hospitalization. Among the respondents who were with MFS, 56.9% had >2 hospitalizations.

There were significant associations between number of hospitalizations (X2=41.026; df 1; p<0.001) with MFS.

The odds of MFS patients with more than 2 hospitalizations are 18.5 times higher than in patients with less than 2 hospitalizations (AOR=18.487, 95%CI=4.573-74.735). The findings of this study in history using inpatient healthcare facilities concur with most studies (Bartels, 2000; González-Pinto et al., 2011a; Tohen et al., 2003). Tohen and colleagues also highlighted that the increasing number of episodes and the presence comorbidity inclosing substance use showed a higher odds of hospitalization. (Tohen et al., 2003)

This study, however did not control for confounding factors that could have been associated with mixed features such as the concurrent substance use, medication adherence, or the polarity of episode that the respondent was in. Nevertheless, the presence of mixed features by itself is already associated with the aforementioned predictors. (Brancati et al., 2019; Giuli Perugi et al., 2015; Young & Eberhard, 2015).

The increase frequency of hospitalization reflects on acute mood state and symptoms severity to the point that it disrupts the patient's routine, work and family relationships. Consequently, this leads to higher economic burden for the patient, and families of patients from possible unemployment.(Bolton et al., 2010). Repeated hospitalizations, additionally contributes to stigma which further amplifies the sufferings of patients and their family. (Staring et al., 2009)

Hence, increasing number of previous hospitalization and its significant association with mixed features is an important predictor for Mixed feature specifier within both MDD and BD.

5.3.3 Pharmacological Treatment

Response to treatment varies with different patients. Studies shows that patients with lesser economic resources, higher interpersonal conflict, minority-status, poorer functionality and quality of life are less responsive to antidepressant treatment.(Thase, 2011)

A narrow and stringent definition of Mixed state in DSM IV, IV_TR has led to a misdiagnosis or perhaps under diagnosis of mixed Depression, Hence most patients with subthreshold manic symptoms within the depressive episode are erroneously treated or perhaps undertreated perhaps with trials of monotherapy antidepressants.(Hirschfeld et al., 2003). Additionally, it has been demonstrated that approximately 25%-50 % of patients who are first seen for Major Depressive Disorder may in turn have bipolar features.(Angst, 2006; Ghaemi et al., 1999)

The National Depressive and Manic Depressive Association conducted a survey among 4192 patients with Bipolar Disorder proved that 69 % of them has a mean consultation by 4 different physicians before suitable treatment and appropriate diagnosis was made.(Nusslock & Frank, 2011). Additionally, the same survey revealed that about 30 % of them waited an average of 10 years before a correct diagnosis was made.

Similarly Ghaemi and colleagues also found that the correct diagnosis of Bipolar spectrum disorder came about 7.5 ± 9.8 years later after the diagnosis of Unipolar Depression was made.(Ghaemi et al., 1999).

Likewise, in this study, majority (59.5%) of respondents had more than 2 trials of medications. Among the respondents who were with MFS 46.6% had >2 trials of medications. There were significant associations between trials of medications (X2=29.540; df 1; p<0.001) with MFS.

The increased failure rate of pharmacotherapy has higher negative implications to the patient in terms of treatment adherence, negative behavior towards treatment which is seemingly another major burden among Bipolar Disorder patients. Furthermore, the higher number of medications failure will also put a strain to the therapeutic alliance between the treating doctor and patient which will further deter an optimum treatment response.(Zeber et al., 2008).

Therefore, a significant association between the number of failed medications among patients with depressive disorder or bipolar disorder, should raise a high index of suspicion of mixed features specifier.

5.3.4 The combination of medications

This study also further looked into the number of medications that the respondents are on currently, 64 (43.2%) are on single medication, 57 (38.5%) are on double medications and 27 (18.2%) are on triple medications which includes anti-depressant, anti-psychotics and mood stabilizers. 85 (57.4%) of respondents are on single anti-depressant, 70 (47.3%) are on single anti psychotics and 96 (64.9%) are not on any mood stabilizers. Among the respondents who were with MFS,50% are on >2 medications.

There were significant associations between total number of medications on (X2=42.338; df 1; p<0.001) with MFS.

It is evident, that pharmacotherapy among mixed features is challenging and requires tactful consideration as there is a need to treat both the depressive and manic/ hypomanic entity concurrently. Guidelines and studies have suggested concurrent use mood stabilizers, and atypical antipsychotics as an alternative to monotherapy.(Fagiolini et al., 2015; Goldberg, Brooks, et al., 2009; Vieta & Valentí, 2013). Furthermore, similar to the findings of this study, STEP-BD trial found that an average of patients with Bipolar Disorder achieved remission with atleast 2.05 medications, among which are Atypical antipsychotics and Mood Stabilizers.(Al Jurdi et al., 2008). There are evidences that signify the association with number of medications across the different states of mood disorder. The pure depressive state is associated with a higher number of medications prescribed, followed by the mixed state as revealed by a prospective study by Woolley and his colleagues.(Golden et al., 2017).

However, this study did not consider other confounding factors that could have led to the results obtained such as medication adherence, comorbidities and severity of symptoms. Among the medications that are associated with polypharmacy within the above study, are mood stabilizers, Anti-depressants and benzodiazepines. However, in this study, the concurrent usage with benzodiazepine and the requirement for polypharmacy across different mood states was not evaluated. Additionally, it is also interesting that, Lithium was found not to have a significant association with combination of >3 medications in depressive state and mixed state within as opposed to Hypomanic state in BDII. (Golden et al., 2017)

Contrastingly, a French study showed that pure mania and mixed mania were characterized by a higher rate Antimanic combination therapy for a period of 2 years.(Azorin et al., 2009).

Older treatment guidelines have advocated the initiation of monotherapy in treating acute manic phases. The higher incidences of combination therapy among acute manic patients could be explained by the mixed occurrence among this group of patients which are harder to stabilize. This has led to advancement and revision of newer treatment guidelines (Morriss et al., 2014)

Similar prescription patterns of antidepressants were seen among the European cohort and the French cohort which showed high rate of antidepressant prescription among the Bipolar Disorder. (Azorin et al., 2009; Rosa et al., 2010). This interesting evidence disputes the various literatures points out contraindication of antidepressant treatment during mania, concerns of treatment emergent mood switches and rapid cycling.(Fountulakis et al., 2007; Truman et al., 2007).

Although, this study did not compare patterns of antidepressant prescription across the mood states and the patterns of combination in mixed features, the majority of the respondents are on single antidepressant treatment and most of them are also on antipsychotics. This could be explained by the practice of prescribing medications according to treatment guidelines that is adhered by the Medical officers within the Hospital Bahagia.

The prescription of medication in HBUK is closely monitored and supervised by different levels of expertise, including psychiatrist, pharmacist and senior pharmacist who also diligently adhere to the national guidelines such as Malaysian Clinical Practice guidelines, and National Prescription Guidelines. Therefore, complex polypharmacological treatment may not be as high as in other studies.

5.3.5 The use of Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) has shown to be highly successful in terms of achieving response and remission for mood disorders especially in depressive states. In fact, it's use has been recommended in widely in many International guidelines of Mood Disorders.(Daly et al., 2001; Dierckx et al., 2012; Goldberg et al., 2007; Yatham et al., 2013).

This study has revealed that more than 90% of the respondents did not have any history of ECT in the past. This corresponds to the findings of several studies that examined the practice of ECT across Asian Countries and found that Schizophrenia was the most common indication for ECT, while the fraction of mood disorder was much smaller.(Agarwal, Andrade, & Reddy, 1992; Kramer & Hsin-Tung Pi, 1990; Xiang et al., 2015).

ECT is mostly used as an adjunctive treatment to achieve remission in Mood disorder and despite the numerous evidence of its efficacy, this practice in Asian countries are much lower compared to other parts of the world.(Chanpattana & Kramer, 2004) This could be explained by the stigma revolving around the use of ECT, by the patient and their families. Clinicians face great challenges in order to obtain consent for the ECT treatment. (Griffiths & O'Neill-Kerr, 2019)

Patient's perspective of ECT is more complex than simply its efficacy in reducing the symptoms of depression; perspectives encompass fears, stress before and during treatment, possible side effects (especially memory loss, confusion, loss of cognitive ability), stigma, and regaining a sense of self and reality (Koopowitz et al., 2003)

Among the respondents who were with MFS, 77.8% had history of ECT. There were significant associations between history of ECT ($X2=10.590$; df 1; $p=0.001$) with MFS.

These findings correspond with the findings obtained by other International studies.(Fagiolini et al., 2015; Medda et al., 2010).

Mixed symptoms as depicted in this study and other studies globally have more severe episodes. Additionally, it is also associated with a more protracted illness and psychosis and greater risk of suicide.(Giulio Perugi et al., 2001)

The sample in this study, was based on outpatient cohort within HBUK, hence it could be postulated that patients who are more severe in symptoms may not have been well represented. Therefore, it could be indirectly inferred that, if the sample population was widened to both inpatient and outpatient, a higher rate of ECT would have been observed. Furthermore, this study excluded patients with psychosis which could have yielded a higher incidence of ECT as well.

ECT has been shown to be effective in most studies of MFS in mood disorder alongside with the challenges faced in managing this group of patients, the significant association that has been demonstrated in this study, is valuable for future researches and enhancing clinical practice as well.

5.3.6 Suicidal Attempts

Among the major psychiatric illnesses, Mood disorders are among the leading causes of suicidal behavior.(Angst et al., 2010; Sato et al., 2003). Suicide is a major public health concern across the world.

WHO in its initiative of Suicide prevention, SUPRE , has denoted that approximately one million people die from suicide annually and further estimated that 10–20 times more people would attempt suicide worldwide.(World Health Organization, 2018).

The situation of suicide in Malaysia is equally worrying, as the rates have increased by 60% o

over the past 45 years. (Sinniah et al., 2014)Furthermore, self-inflicted injury is a rising concern as it represents 1.4% of the global burden disease in 2002 and it was expected to be doubled by 2020.(TB Alliance, 2010)

A much earlier study conducted in 1997 by Cosar found retrospectively among the patients who have committed suicide, 43.3% have a history of previous suicide attempt.(Coşar et al., 1997). Unfortunately , this figure turned out to be much higher, in a more recent study carried out in Hong Kong in 2010.(Law, Wong, & Yip, 2010).

In Malaysia, it was found that out of 243 of suicide victims , 21.4% had a history of previous suicide attempts.(TB Alliance, 2010) However, this figures remain debatable, as death by suicide are mostly hidden and underreported owing to several pertinent motives such as religious attitudes and social perceptions, and fear of stigma towards the family members of deceased. Furthermore, there have been worldwide reports stating the rates of underreporting ranges from 20% to 100 %.(Bertolote et al., 2004).

In this study,75.7% of the respondents had no history of suicidal attempts which signifies a much lower rate compared to other studies. This corresponds to the data captured by National Suicide Registry Malaysia.

Among the respondents who were with MFS, 63.9% had history of suicidal attempts and the associations obtained were statistically significant. ($X2=26.570$; df 1; $p<0.001$). There are well established evidences to show strong association between suicidal risk factors and mixed symptoms. (Balázs et al., 2006; Bonnín et al., 2012; S. Miller et al., 2016; Popovic et al., 2015; Shim et al., 2015; Swann et al., 2013). A study by Song and

colleagues, the presence mixed episodes strong predicts suicide attempts alongside with a study by Valtonen.(Song et al., 2012; Valtonen et al., 2007).

However, in this study, the history of suicide attempt was obtained from the account of patients themselves and can be confounded by recall or reporting biases. Furthermore, there are several other factors associated with suicide attempts, among which are comorbidity, influence of substance, type of medications, the mood episode associated with the suicide attempt and other psychosocial factors that influence the act itself.

Nevertheless, mixed feature specifier itself is strongly associated with the aforementioned risk factors for suicide attempts which alongside with evidences demonstrated in majority of the studies further amplifies its significance. On top of that, the individual symptom profile of such as irritability, impulsivity, psychomotor agitation, racing thoughts and emotional lability adds on to the risk that Bipolar and Depressive patients already have.(Pringuey et al., 2013; Swann et al., 2005; Undurraga et al., 2012; Vázquez et al., 2018)

Although, the rates of suicidal attempts in MFS I this study is not an accurate representation of the suicide rate in the Malaysian population, the significant association found in this study warrants deeper exploration and a more thorough assessment for suicide risk factor during clinical practise.

5.3.7 Substance use

Substance use commonly occurs among psychiatric disorders especially in Mood Disorders. In this study, the majority of patients reported an absent history of substance abuse. (72.3%). This finding contradicts many other studies that has a converging results that point out strong associations of mood disorder with substance abuse. Kessler and

colleagues as early as in the 1990s have found that Bipolar Disorder have seven times more likely to be acquainted with substance abuse. (Kessler et al., 1997). This discrepancy could be possibly due to reporting or recall biases. The history obtained mostly were from the account of patient and the records, which could have been concealed or missed.

This study demonstrated similar findings across few other international studies that showed significant difference of substance use among mixed feature specifier whereby majority of the MFS group has reported of substance abuse before (56.1%), ($X2=19.249$;df 1; $p<0.001$).(Reich, Davies, & Himmelhoch, 1974; Swann et al., 2013; Vázquez et al., 2018)

The results in this study stands in contrast with the study by Cassidy and colleagues which found no significant associations between substance abuse and mixed features. These differences could be explained by the retrospective nature of the study, under reporting of patients. Furthermore, the sample population in this study was acute inpatients who may not be forthcoming with their substance use history. (Cassidy, Ahearn, & Carroll, 2001)

The frequent and common occurrence of substance use among patients with MFS makes the treatment and management of this group of patients to be more challenging than it already is. Furthermore, certain types of substance such as stimulants type of substances could mimic symptoms of mania and present concurrently in a depressed patient. (González-Pinto et al., 2011b). Additionally, many studies have shown strong association of substance abuse as a strong risk factor for suicidality.(Borges, Walters, & Kessler, 2000; Pompili et al., 2012).

This study as well as many other studies have shown high prevalence of MFS with suicidality, hence substance use will double the risk for a poorer outcome among this

group of patients. This study however, did not look into the correlation of MFS in MDD separately from BD with MFS in terms of substance use. Additionally, this study also did not address the pattern of substance usage. Nevertheless, this study has pointed out sufficient association of MFS with substance abuse which is shown to be an important predictor of a poor outcome.

5.3.8 Compliance to medications and treatment

Medication adherence or compliance is an important factor that affects the outcome and severity of an illness. This entity contributes to one of the biggest challenge in the treatment of mental illness.(Dickson, 1986; Haynes et al., 2008). Literature search, has presented a strong association of mood disorder be it Major Depressive Disorder or Bipolar Disorder with significant rates of poor to complete noncompliance to treatment of follow ups.(Alan D Lopez et al., 2006; Dickson, 1986; DiMatteo et al., 2000). In fact, studies have reported that the rate of treatment non- adherence among Bipolar Disorder patients ranges from 20% to 66% with a mean prevalence of 44% .(Berk et al., 2010; Lingam & Scott, 2002)

Interestingly, the findings in this study stands in contrast with many studies that showed majority of patients, [99 (66.9%)] with a good compliance to medications and treatment which.

This result could be contributed by the sample population that comprises of outpatients, who have been mostly in remission as the other parameter within this study indicate. There are many variables that are associated with poor medication adherence. Among which are the factors relating to the illness itself, such as illness severity, insight, symptoms frequency and comorbidity. (Buckley, 2006; Haynes et al., 2008; Husted, 1999)

Poor compliance could be further attributed to the choice and type of pharmacotherapy administered as well. Many studies have underscored that, the complexity of pharmacotherapy, adverse effects from the medications and treatment efficacy plays a

impactful role in treatment adherence.(Lingam & Scott, 2002; Scott & Pope, 2002; Sportiche et al., 2017; Thase & Sachs, 2000).

A study by Zhang and colleagues who found that during higher symptom severity or relapses, the perceived adverse effect from pharmacotherapy is higher and thus further contributing to treatment non-adherence.(Zhang et al., 2014)

Therefore, the remitted state in this sample population could explain the low prevalence of treatment non-adherence in this study.

Additionally, most studies that reported a high prevalence rate of treatment discontinuation among mood disorder patients, did not control for other potential confounding factors such as family support, socioeconomic characteristics, therapeutic alliance which are also important predictors in treatment adherence.(DiMatteo, 2004; Krueger, Berger, & Felkey, 2005; McCabe et al., 2012; Miller & DiMatteo, 2013; Zeber et al., 2011).

In this study, there were significant associations between compliance to treatment ($X2=4.310$; df 1; $p=0.038$) with MFS. Among the respondents who were with MFS, 40.8% had poor compliance to treatment. This finding is in line with the EMBLEM study and other studies that showed high prevalence of poor compliances among patients with mixed symptoms.(Azorin et al., 2009; Goldberg, Perlis, et al., 2009). It has been apparent from data in this study along with evidences other studies that Mixed symptoms are associated with a high number of variables that could also contribute to poor treatment compliance among patients. Therefore, a significant positive correlation is expected among these two variables. Nevertheless, in this study, the data was obtained from a self-report method from the patients themselves. The prevalence of medication non-adherence could presumably be much ~~of~~ higher, as it could have been underreported. Therefore, a

more precise way of assessing medication adherence would be to use a valid scale. Furthermore, this study did not control for other confounding factors to medication adherence.

Nevertheless, the results obtained in this study has shown that medication adherence is strongly associated with Mixed Feature Specifier in mood disorders which could further impact upon the treatment and outcome of patients.

5.3.9 YMRS score and MADRS score

Most of the respondents had a YMRS score of being in remission – 106 (71.6%). There were significant associations between YMRS score (X2=16.799; df 1; p=0.001) with MFTS. This study concurs with other studies that demonstrate higher YMRS scores among Mixed Features Specifier especially in Depressive Episode expectedly.(S. Miller et al., 2016; R.S. et al., 2014). These findings were similar also for MADRS scoring, 51 (34.5%) was asymptomatic and 71 (48.0%) had mild depression.

There were significant associations between MADRS score (X2=43.525; df 1; p<0.001) with MFS.

This study was conducted among the outpatients' attendees in HBUK, which could explain the higher number of respondents who are in remission. Furthermore, this study is based upon voluntary participation, which may not represent the true population in terms of medication and follow up compliance which are among the prerequisites to achieve remission.(Strassberg & Lowe, 1995). Convergent to other studies, this study did not look into the differences in terms of symptoms severity comparing each mood episode and also across different items in the scales. There has been evidence of significant proportion of patients with MFS to have prominent irritability and language and thought

disorder (McIntyre et al., 2014). These symptoms could easily be undermined and overlook by clinicians owing to the overlapping criteria of DSM 5 for depressive Disorder.

Additionally, severity of an illness has a direct impact to the functionality of an individual. Studies have shown that Bipolar Depression has a higher likelihood to have prolonged and sustained disability. (Arvilommi et al., 2015; Zimmerman et al., 2010). This study as well as the findings of few other studies globally shows a lesser remission rate associated mixed features specifiers.

This is a reliable indicator of a poor outcome associated with mixed features specifier. Furthermore, studies that have used YMRS and MADRS to measure treatment efficacies found that there are significant differences with different agents of treatment to achieve a better remission rate in mixed features.(McIntyre et al., 2013)

5.4 QoL in respondents with MFS

There has been a paradigm shift in the aim of treatment in mental health service policy from symptom reduction to a more holistic approach which entails improvement in quality of life to recovery.(HM Government, 2011). This study attempted to enumerate the quality of life among patients with Mixed features specifiers among MDD, BD 1 and BD 11 as compared to the group without Mixed features specifiers.

In this study there were significant differences between the mean scores in respondents with MDD and respondents with MDD MFS, as well as BD MFS and BD without MFS in all 4 domains which are physical, social, psychological and environmental. These domains correspond to the definition of Quality of life which takes into consideration of an individual's performance in daily activities such as work, play, relationship and

health.(Ishak et al., 2011) This seems to be concordant even across different types of scales that are used to assess quality of life.(Allison, Locker, & Feine, 1997; Dow et al., 2007; Lee Mortensen et al., 2015; Mazza et al., 2012). This study utilized the WHOQOL-Bref which is a self-administered questionnaire to assess the physical, psychological, social, and environmental aspects of QOL. This questionnaire has 26 items which are rated on a 5-point likert scale. It was chosen as it was suitable across multilingual, multicultural and has been tested across 15 different field centers.(Harper et al., 1998; WHO, 1998).

There are well documented evidences that shows depressive episodes in Bipolar Disorder having a huge impact on quality of life of patients. This study as well as many other studies found a significant association of poorer quality of life in mixed episodes compared to depressive episodes. Additionally, the findings in this study corresponds with the findings of Vojta and his colleagues who found that dysphoric mania as this study identifies Manic episodes with concurrent presence of depressive symptoms showed lower mean scores in terms of quality of life among the mixed symptoms group. Although, this study, utilized EuroQOL scale which is different from WHOQOL-BREF, it is also a validated self-reported scale. Among the key limitations of the study by Vojta, was the predominance of males within the sample population, nonetheless, this study also tried to asses quality of life using clinician rated scales as well to reduce reporting bias.(Vojta et al., 2001).

Apart from the symptoms Mixed Features Specifiers that differs from pure mania or pure depression group, there are other factors that affect the quality of life of patients with mood disorders. Among them are, presence of physical illness, comorbid of substance use or abuse, family background and acceptance, comorbidity with other axis 1 disorders,

financial status and adverse life events and ongoing stressors. Furthermore, self-stigma associated with severity of illness, duration of hospital stay, number of previous hospitalization and poor work productivity also is an important determinant for poor quality of life associated with Mood disorders.(Allison et al., 1997; Evans et al., 2007; Kauer-Sant'Anna et al., 2007; Mashiach-Eizenberg et al., 2013).

Therefore, in order for a more accurate representation, these possible confounding factors has to be controlled for which was not done in our current study. Additionally, the correlation between the severity of YMRS scores and MADRS scores with the domains of QOL may depict a better understanding.

As reported by Gazalle and colleagues, there is significant impairment in social domains of the WHOQOL in higher YMRS score.(Gazalle et al., 2007). On the contrary to one's expectation, depressive episode with the presence of concurrent symptoms of elevated mood has been shown to have significant functional impairment.

Nevertheless, the result in this study has provided a foundation for future research to look into this aspect as it has shown that the presence of Mixed features specifier is strongly correlated with poorer quality of life across all domains.

Although this is a cross sectional study, that looked into the current episode that the patient is in, it is apparent that patients who are experiencing mixed symptoms recognize their deterioration in quality of life and are able to compare them in times of euthymia,

mania or depressive episode they experience in the past as due to the self-reported nature of the questionnaire which requires active participation of the respondents.

Though there are several methodological limitations to this study in terms of enumerating the quality of life within Mood disorder patients with Manic Feature Specifier, this study has provided a stepping stone, that demonstrated that apart from Depression or Depressive Episode that has a high predictor of poor quality of life and outcome, patients who experiencing Mixed features specifier has a comparable impairment and disability.

The significant low mean scores that is shown in the work domain in this study, reflects on the high financial burden, low income group and higher dependence on financial aid. (Kleinman et al., 2003). This correlates with the findings of low average wage among respondents with MFS in this study.

In summary, the data obtained in this study, provides further support that Mixed Feature Specifier has significant association with poor quality of life as perceived by the patients themselves. This should be targeted in management and treatment strategies in order to achieve the aim of recovery in patients with mood disorders.

CHAPTER 6

CONCLUSION AND RECOMMENDATION

6.1 Conclusion

In this study, we found that Mixed Feature Specifier is a crucial entity in patients with Major Depressive Disorder and Bipolar Disorder. Along with the parent symptoms of the mood disorder, MFS has a significant impact on the course of illness.

Furthermore, we found a considerable prevalence of MFS among Bipolar Disorder and Major Depressive Disorder where among the 148 respondents that were recruited, the overall prevalence of MFS among Major Mood Disorder was 29.8%. However, the prevalence depicted in this study should be interpreted by keeping the limitations in terms of methodology in mind.

In this study there are significant associations in terms of certain sociodemographic characteristics such as ethnicity, marital status. The course of illness and clinical characteristics too has been shown to be implicated by the presence of MFS. There are significant associations demonstrated between the presence of MFS with variables such as familial history of mood disorder, history of suicidal attempts, history of ECT, trials of medications, number of medications patients are on, number of previous hospitalizations, history of substance use and compliance to medications

From the results that we obtained, it could identify some predictors associated with MFS which were significant in the sociodemographic factors and clinical characteristics such as amount of income, substance use and number of hospitalizations.

It was demonstrated in this study that the presence of MFS in mood disorder has significant negative implication in the quality of life of patients as measured by a validated self-reported scale across all the four domains which are Physical, Social, Psychological and Environmental domains. These domains are pertinent in facing the daily life among patients.

This study also looked at symptom severity as another component of associating factor and found that MFS has significant associations with higher scores in YMRS and MADRS.

As a conclusion, we fail to reject the alternate hypothesis that there are sociodemographic and clinical characteristics associations with MFS. We also failed to reject the alternate hypothesis that there are significant differences between the QoL of MFS patients and non MFS patients.

6.2 Limitation

There are several limitations identified in this study which are enumerated below.

1. The sample size in this study was rather limited which could contribute to a lesser power of the study and a reduced precision. A larger sample size would be preferred to improve the precision.
2. The design of this study is cross-sectional. Therefore, the causal relationship between MFS in mood disorder could not be ascertained with the associating factors. This study design only enables to show significant association between the variables.
3. The sample population in this study is focused on a single location. HBUK is a psychiatric institution and is located in the outskirts of the country. Hence the catchment area, may not be a well-represented sample to infer to the general population within the countries due to the variation of sociodemographic factors.
4. This sample population only involved the outpatient group, hence only stable patients were recruited in this study. Therefore, the more respondents would be in remission or report for mild symptoms. Additionally, the number of medications, types of medications and the course of illness may not be accurate to represent the true scenario within the general population.
5. This study only involved a single researcher, hence, there could be researcher bias, as there is a tendency to skew according to the reseacher's preferences.
6. There are other biases as well identified in this study, such as reporting bias where respondents had to give accounts of substance usage, personal information of demographics such as wage which are prone to have underreporting and may not depict the true prevalence. Additionally, there could also be recall biases, where

patients had to give certain information such as number of previous hospitalization, or ECT which is subjected to patient's memory.

7. The limited number of researches on Mixed Feature Specifier in the Asian region and being the first study to look into the Mixed Feature Specifier makes it difficult to compare the related demographics and clinical characteristics of the result in study.

6.3 Recommendations for Future Studies

Future studies on MFS should be more detailed and specific using designs such as case control or cohort study. A cohort study will be the one that allows us to calculate incidence, relative risk, risk differences and attributing risk and will be more reflective over a certain period of time rather than a specific period such as in this cross sectional study.

This study covers two characteristics, namely socio-demographic and clinical characteristics. More MFSs study in the future should be done in more settings to study associations and predictors from other group factors.

Certain variables in this study was based upon, recollection and history obtained from the patient, therefore a more accurate assessment with related scales could be administered in future researches especially among the variables of suicide attempts and substance use.

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