

## Retrospective Study of the Prevalence of Recurrent Aphthous Ulcer

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### Abstract

The prevalence of Recurrent Aphthous Ulcer (RAU) is varied in different regions of the world. There is insufficient survey in prevalence of RAU in Malaysia as the only latest figure available is about 18 years ago. This study aimed to measure the prevalence of RAU in patients attending Dental Clinic-college of dentistry within 5 academic years and to know the distribution and relation of RAU based on the most common type of RAU, gender, race and age range.

A retrospective cross-sectional study based on the confirmed case of RAU from the students' Oral Medicine logbooks and case sheets from the attended patients' folder to Oral Medicine Dental Clinic- college of dentistry from academic year 2012/2013 to 2016/2017.

160 patients were diagnosed of RAU. 0.42% of prevalence among the total patients was found to have RAU. As compared between the Oral Medicine cases, patients that were diagnosed with RAU shows prevalence of 11.13%. The most common type was minor RAU (96.9%), followed by major (3.1%) and no patient was presented with herpetiform type. Based on gender, females showed more predilection of RAU compared to males with 60.6%. Age range of 20-29 showed the highest percentage of 71.3 % and Malay showed the most common race of RAU compared to Chinese and Indian which was 97.4%.

The results indicate there is a relation between the type of RAU, age, gender, race and with the prevalence of RAU. Further studies should include larger sample size with a wider range of populations.

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### Introduction

One of the most frequent inflammatory ulcerative conditions of oral mucosa is recurrent aphthous ulceration (RAU) that is characterized as painful round shallow ulcers surrounded with well-circumscribed erythematous margin and yellowish-grey pseudomembranous centre. It is preceded with burning sensation 24 to 48 hours before the ulcers appear.<sup>1</sup> There are three clinical classifications of RAU, which are minor, major and herpetiform. The minor aphthous ulceration is once known as 'Mikulicz's aphthae',

is small, less than one cm in diameter and heals within 2 weeks without leaving any scars.<sup>2</sup> Whereas Sutton's aphthae or periodontitis mucosa necrotic recurrens are the previous terms used to describe the major aphthous ulceration, which is larger (1-3cm in diameter) and heals with scars within 2-6 weeks.<sup>3</sup> Herpetiform aphthae or Cooke's ulcers are small, 1-3mm in diameter and can have up to 100 ulcers in a single recurrence.<sup>4</sup>

According to British Journal of Oral and Maxillofacial Surgery, minor aphthous ulcer is the most common type which involves 80% of patients, with less than 5mm in diameter, small, round or oval, usually with a grey-white pseudomembrane and an erythematous halo. Major aphthous ulcers affects 10% of the patients, in which this kind of ulcers may be more than 1cm in diameter with irregular outline. They are usually single and often affect the fauces.

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Herpetiform ulceration contributes about 1-10% of the aphthous ulcers.<sup>5</sup>

Previous study showed that RAU affects approximately 20% of the general population, but there are variations about 5% to 66% among different nations.<sup>6</sup>The prevalence of RAU was 28.2% in Sulaimani city of Iraq,<sup>7</sup> whereas in India, the prevalence is 0.48%.<sup>8</sup>Based on a study conducted by Zain et al in Malaysia in 2000, shows that the prevalence of RAU is 0.5%.<sup>8</sup>In a cross-sectional studies which has being done before, RAU has more predilection in women, in individual younger than 40 years, in whites, in non-smokers and high socioeconomic status group.<sup>6</sup>According to a study done among Indian population by Patil et al in 2014, overall prevalence was 21.7%.<sup>9</sup>It usually affects the non-keratinized or poorly keratinized surfaces of the oral mucosa such as labial and buccal mucosa, maxillary and mandibular sulcus, unattached gingiva, and soft palate, floor of mouth and ventral surface of the tongue. The aetiologies of RAU remain unclear but it is highly associated with both environmental and genetic factors such as psychological stress, trauma, infection, allergic and nutritional deficiencies.

The aim of the study is to measure the prevalence of RAU in patients attending Dental Clinic College of dentistry within approximately 5 academic years as the only latest figure available for prevalence of RAU in Malaysia is about 18 years ago. At the same time, this research is also intended to know the distribution and relation of RAU based on gender and age as well as to identify the most common type of RAU occurs in patients that attended Dental Clinic-college of dentistry. Although RAU is not a very serious condition, it causes pain intraorally which interferes with meal intakes for weeks that can adversely affects individual's quality of life due to inadequate nourishment, as well as his daily activity.<sup>6</sup>

## Materials and methods

### Study design

This was a quantitative, categorical retrospective cross-sectional study design conducted among patients attended Oral Medicine Dental Clinic college of dentistry from academic year 2012 to 2017.

### Ethical consideration

The ethical approval was obtained from IIUM Research Ethical Committee (IREC) with ID number 668.

### Data collection

The study was started by using the Oral Medicine logbooks to trace the attended patients' folder. The data from patients' case sheet files that include the medical and dental history and relevant etiological factors were recorded. The Oral Medicine specialists who supervised the Year 4 and Year 5 dental students would confirm the diagnosis of RAU. The guidelines to diagnose RAU during oral examination were according to "Guide to epidemiology and diagnosis of oral mucosal diseases and conditions" by the World Health Organization.<sup>9</sup> The criteria were:

- a) The presence of ulcers confined to non-keratinized mucosa or tongue with 1-4 ulcers during one episode. The ulcers are well defined and covered by a grey-white or yellowish fibrinous coating surrounded by an erythematous halo. The subjects report a history of recurrence which heals in 1-2 weeks without scarring (minor form), or in a few cases;
- b) The presence of 1-2 ulcers for each episode occurring on any part of the non-keratinized mucosa or fauces with a predilection for the tongue in some patients. The ulcer feels indurated and heals with scarring (major form). The subjects report a history of recurrence, which heals in several weeks.

Data collection of RAU patients and their details which were the age groups, gender, types of aphthous ulcer and site of lesion were analysed by using descriptive statistical analysis.

All adult male and female patients whom is clinically confirmed with recurrent aphthous ulcer are included in the data collection. Patients who are confirmed to have systemic ulcerative mucocutaneous lesions, traumatic and iatrogenic ulceration are excluded from the sample.

### Data and statistical analysis

Collected data was entered into Microsoft excel prior to the data entry and analysis by SPSS 16.0 version.

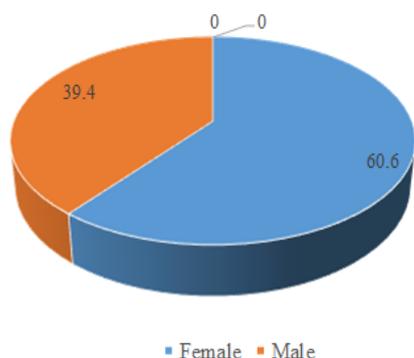
## Results

The total number of patients registered at the college of dentistry Dental Polyclinic in 5 consecutive years (2012-2017) was 57,937 by which 2165 of them have attended the Department of Oral Medicine and Oral Pathology. The descriptive data analysis was used to analyse the data from the attended patients' dental continuity sheets. 0.42% among the total patients was found to have RAU. As compared among the Oral Medicine cases, patients that were diagnosed with RAU was 11.13%.

Among the patients who diagnosed with RAU with complete required data (160 patients), the most common type is minor RAU (96.9%), major (3.1%) and no patients were presented with herpetiform type (Table 1). In distribution of RAU according to gender, females showed to have more predilections to have RAU compared to males with 60.6% (Figure 1). Relationship between RAU with age range showed the most common to occur in the second decade of life with 71.3%. The following chart shows the respective distributions in the other age range of patients (Figure 2).

	Frequency	Percent (%)
Minor RAU	155	96.9
Major RAU	5	3.1
Total	160	100

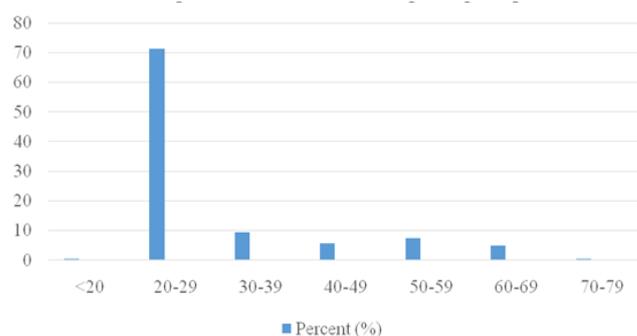
**Table 1.** The most common type minor RAU (96.9%), and major (3.1%).



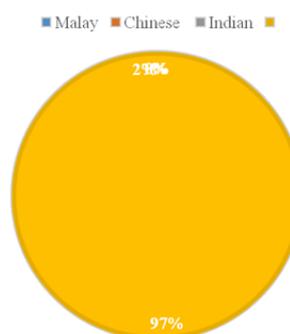
**Figure 1.** Distribution of RAU according to gender.

Other than relationship between the RAU with gender and age range, there is also another finding to find the distribution of RAU with race of

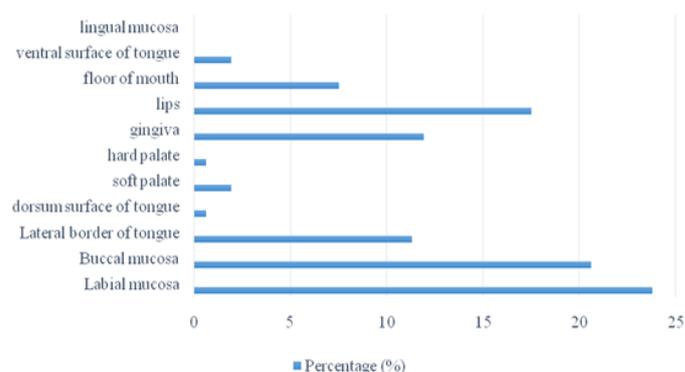
patients. Result shows that Malay is mostly affected by RAU. Following pie chart shows the data recorded (Figure 3). The distribution of RAU according to different sites of oral cavity is also recorded in the following chart in which the labial mucosa is the most common site for formation of RAU, followed by buccal mucosa and the lips (Figure 4).



**Figure 2.** Relationship between RAU and the age range of patients.



**Figure 3.** Relationship between the RAU with gender and age range.



**Figure 4.** Distribution of RAU according to sites.

## Discussion

RAU is presented with painful ulceration and associated with itching, burning sensation and

interfering with eating and swallowing as the actions will exaggerate the pain. The prevalence study of RAU can give an insight regarding the proportion of population having the condition, the demographic associations, the possible predisposing factors and their respective management and treatment for RAU.<sup>10</sup>

Clinical examination and patients' history are the fundamental steps in order to diagnose the RAU and to further classify them into different forms. Even though RAU is very common to occur, the exact aetiology is still unknown but many possible etiologic agents and predisposing factors can be associated with RAU. The occurrence of RAU can be precipitated or related with allergies, local trauma, genetic, nutritional deficiencies, hematologic abnormalities, hormonal influence (related to menstrual cycle), infectious agents and stress. Nevertheless, those factors and possible aetiologies still have poorly supported evidence.<sup>11</sup>

In a study conducted by Zain et al (2000), prevalence of RAU was 0.5%. In relation to race and ethnics, the RAU found to be the highest in the indigenous people of Sabah and Sarawak (1.2%), Chinese (0.7%), Malays (0.5%) and Indians (0.1%).<sup>12</sup> There was not much different with the prevalence of the RAU in our study which is 0.42% and the study by Malayil(2014) also reported the prevalence of RAU was 0.48%.<sup>3</sup> However for the relationship between prevalence of RAU with the race, the result was different, in which the greatest number of patients having RAU was among the Malay population as compared with study done by Zain et al (2000). Whereas, Kareem et al (2015) conducted a research to study the prevalence of aphthous ulceration among patients attending Oral Diagnostics Clinic at University of Sulaimani found that 15% of subjects were having the aphthous ulceration.<sup>7</sup> In conjunction to our research, the percentage of patients that were having RAU to the total number of patients visited to Department of Oral Medicine was 11.13%. Safadi in 2009 studied the prevalence of recurrent aphthous ulceration in Jordanian dental patients by conducting a survey and found that 78% of subjects have experienced history of having recurrent aphthous ulceration. 92% of subjects claimed of painful symptom, and 82% said that the lesion interfered with eating.<sup>6</sup> Abdullah et al (2013) in his study of prevalence of recurrent aphthous ulceration in

patients attending Piramird dental specialty found that life time prevalence of RAU experience was 28.3% among 1000 subjects,<sup>6</sup> while Patil et al (2014) in her study among patients attending Department of Oral Medicine and Radiology showed that the prevalence was 21.7%.<sup>13</sup>

There is strong association between the gender with the formation of recurrent aphthous ulceration. Study by Safadi (2009), Abdullah (2013), Malayil(2014) and Patil et al (2014), reported that females had more predilection of having RAU as compared with males, which is parallel with our research finding. Conversely with study by Kareem (2015), the result showed that males were having RAU more than females with percentage of 56%. Whereas Zain et al (2000) stated that there was no significant difference in distribution of RAU in men and women. In association with gender, the conducted study found female subjects had more predilections to have recurrent aphthous ulceration (82%) than the male subjects (73%). As reported by McCullough et al (2007), the onset of recurrent aphthous ulceration in female patients was related with their menstrual cycle, pregnancy and dysmenorrhea (symptom of painful menstruation) however during pregnancy RAU was improved.<sup>14</sup> Study by Balan et al (2012) regarding symptomatic changes in healthy young menstruating women during normal hormonal turnover revealed that RAU was been affected by 30% of subjects, 5% herpes labialis and 8% was having gingival bleeding, burning sensation of oral cavity, and swollen salivary glands. According to various studies that have been conducted, it was found that oral mucosa is susceptible to changes in respond to fluctuations of sex hormones which lead to alteration of host immune response. Several researches have verified the association between RAU and menstrual cycle, in which it was found that the RAU is mostly occurred during luteal phase between ovulation and menstruation that is modulated by changing levels of progesterone. Action of progesterone on tissues that previously subjected to oestrogen contributes to the eruption of RAU.<sup>15</sup> Exogenous antigens as well as stress are proposed to be the precipitating factors to the formation of RAU in females during this period. Psychological stress during premenstrual period is also be a part of the cause for the lesion.<sup>16</sup>

Most of prevalence of RAU studies observed the relationship with different age groups. The result from our research found that the second decade of life had the highest prevalence of having RAU. This is supported by study done by Zain et al (2000), Kareem (2015) and Abdullah (2013) with age of 25-34 years old, 21-30 years old and 20-29 years old respectively. While results from Malayil(2014) and Patil et al (2014), the highest age groups having RAU were second to fifth decades of life and third and fourth decades of life respectively. This may be related with emotional and psychological stress among this age group. Result found that 50% of subjects related the lesion with stress, whereas 68% reported that tiredness was not the causative factor in the study by Abdullah (2013). 66.4% of them claimed that their family members were also suffered from the recurrent aphthous ulceration. Patil et al (2014) found that 53.8% of subjects of having RAU were associated with stress and 25% of them were related to nutritional deficiency.

Extra finding from this study is that the labial mucosa was the most common site for the formation of RAU, followed by buccal mucosa and lips. In conjunction by Kareem (2015), he found that the most common site is the internal surface of lower lip followed by buccal mucosa, which is parallel with findings by Abdullah (2013), 73.10% of RAU located at lip and buccal mucosa. Whereas Malayil(2014) stated that the most common site was labial mucosa, followed by tongue and buccal mucosa.

Regarding the associating factors of RAU, Sun et al (2015) in an article of 'Significant Association of Deficiencies of Hemoglobin, Iron, Vitamin B12, and Folic Acid and High Homocysteine Level with Recurrent Aphthous Stomatitis' revealed that there are significant association between the nutritional deficiency with RAU, in which RAU patients demonstrated to have abnormally high blood homocysteine level and deficiencies of haemoglobin, iron, vitamin B12 and folic acid. This is supported by a study from Nolan et al, 28.2% of patients with RAU found to have vitamins B1, B2 and/or B6 deficiencies, and Kozlak et al (2010) with his result of the subjects had significantly lower intake of vitamin B12 and folate in daily meal as compared with controls. Therefore, those patients were indicated to have vitamin replacement therapy.<sup>17,18</sup> A higher level of

psychological stress was found in patients with RAU than the control group that has been reported by Gallo et al(2009) which it acts as triggering or modifying factor instead of being the cause of the disease. Stressful events in life such as exam periods, dental treatments and periods of significant changes in life can promote the RAU, by which psychological stress stimulates immunoregulatory activity by increasing the number of leucocytes at the site of inflammation.<sup>19</sup> Other than that, anxiety manifested from stress can lead to parafunctional oral habits, cheek and lip biting causing trauma to oral cavity and forming RAU. Hence, interventions for stress management like relaxation with yoga is thought to be important in order to reduce the rate of recurrence of RAU.<sup>3</sup> Tobacco is known to be as oral cancer, oral mucosal lesions and periodontal disease main risk factor. As in RAU, there was been reported by Hill et al (2010) that patients who stopped smoking usually complain of manifestation of RAU in their mouth.<sup>20</sup> The incidence of RAU was also appeared to be lower in smokers rather than in non-smokers. McRobbie et al (2004) explained that the increase of keratinization of oral mucosa that caused by tobacco has rendered the mucosa to be less susceptible to the ulceration.<sup>16</sup> Based on Akintoye et al (2005) and Natah et al (2004), 24-46% of reported cases to have association of family history with incidence of RAU.<sup>12</sup> Few studies done before assumed that the autosomal recessive of multigene mode of inheritance play major role in RAU formation in conjunction with environmental factors.<sup>21</sup> Moreover, patients that have family history of RAU tend to have more severe form of RAU. This is demonstrated by a study that 90% of a child will have risk of RAU if the both of parents have RAU, while only 20% in children with healthy parents.<sup>21</sup> Kobayashi et al (2005) reported the case of RAU among monozygotic twins<sup>22</sup> while RAU occurrence in 4 members of the same family was studied by Yilmaz and Cimen (2010).<sup>23</sup> These findings support the relation between genetic factor with the formation of RAU. In a study entitled Recurrent Aphthous Ulceration of the Mouth; a study of the natural history, aetiology and treatment discussed that RAU can be associated with systemic disorders such as nutritional deficiencies (that lead to anemia), Behcet's

syndrome, cyclic neutropenia, and HIV infection.<sup>20,24</sup>

In order to diagnose RAU correctly, both clinical history, extraoral and intraoral examination as well as specific examination of the ulcers are crucial. A general practitioner must record the family history, frequency of ulceration, duration of ulceration, number of ulcers, site of ulcers (non-keratinized or keratinized), size and shape of ulcers, associated medical conditions, genital ulceration, skin problems, gastrointestinal disturbances, drug history, edge of ulcer, base of ulcer, and surrounding tissue in the patients that are presented with the ulceration. Whenever there is persistent manifestations of ulceration, investigations such as hemoglobin and full blood count, erythrocyte sedimentation rate/C-reactive protein, serum B12, serum/red cell folate, anti-gliadin, and anti-endomysial autoantibodies can be carried out. During the examination of the ulcer, the consistency of the base and fixation to underlying structures must be evaluated. Patients who are presented with persistent RAU should have follow-up for the underlying hematinic disorders such as full blood count and inflammatory markers and hematinic measurement. Whereas in cases of RAU that have association with systemic condition it is strongly advised to consult with appropriate specialist for further managements.<sup>20</sup>

There are many other diseases that are presented with similar clinical manifestations as RAU. However, those conditions can still be differentiated from RAU with additional symptoms. For example, in case of HSV infections that can be presented with ulcerations usually will be preceded by diffuse gingival erythema and fever as well as prodromal symptoms. Whereas the recurrent HSV are usually can be seen on keratinized oral mucosa. Those key points are important to differentiate with RAU as RAU is not been preceded with prodromal symptoms and it is usually located at movable or non-keratinized oral mucosa such as buccal and labial mucosa, lips, tongue and soft palate. Other viral infections that can be as differential diagnoses are varicella zoster virus, herpangina, and coxsackie virus. Other condition such as erythema multiforme can be presented as ulceration in oral cavity but at the same time, patient will have crusted lips with skin macules and papules. Ulcerative type of lichen planus is clinically similar to RAU but it is

not always painful as what patients with RAU mainly complaint of.<sup>20</sup>

In Oral Medicine Dental Clinic college of dentistry, the patients who are presented with painful RAU are usually prescribed 0.1% triamcinolone acetonide cream to be applied to the area of lesion 3 or 4 times daily which can reduce the symptom of pain and burning sensation. Chlorhexidine gluconate mouthwash with concentration of 0.12% is also prescribed twice daily to the patient in order to reduce the bacteria, to facilitate the healing process of RAU as well as it is also able to reduce the size of ulcer, duration of RAU and the pain. Patients are instructed to rinse the mouth before application and they are advised not to eat, drink or rinse their mouth after the topical application of medicaments. The main goal is treating RAU is to reduce the symptoms, decrease the number and size of the ulcers and reduce the frequency rate and increase the periods of disease-free among the patients. The treatment given depends on the severity of pain from the ulceration, medical history, frequency of recurrences and patient's response to the medication. Therefore, in order to manage and treat RAU, possible predisposing factors in specific patients should be identified and controlled. The underlying possible systemic disorders must be investigated and excluded. Detailed clinical history as well as the investigative procedures such as laboratory test should be done when necessary. Patients that are confirmed to have continuous outbreaks and high recurrent rate of RAU and symptoms (severe pain and difficulty to eat) should be treated pharmacologically with application of local treatments initially.<sup>25</sup> Topical medications that are commonly used to treat RAU are antiseptics (chlorhexidine), corticosteroids (triamcinolone acetonide), anti-inflammatory drugs (amlexanox), and antibiotics (tetracyclines).<sup>26</sup> Potential nutritional deficiencies must be investigated first prior to initiation of medication as Kozlak et al (2010) stated that the number and/or duration of RAU episodes can be reduced by having sufficient intake of vitamin B12 and folate. Traditionally, RAU is treated by glucocorticoids and antimicrobial therapy which can be administered as topical pastes, mouthrinses, intralesional injections and systemically via oral route.<sup>20</sup>

## Conclusions

Recurrent aphthous ulceration is the most common lesions of the oral cavity which mostly affects females and in second decades of life. Among the three types of RAU, the minor RAU is the most commonly to occur. The site of occurrence usually at the labial mucosa, followed by buccal mucosa and lips. In relationship between RAU and race, through this study, Malay is the most commonly to be affected by RAU.

The treatment of RAU is mostly symptomatic due to unclear etiopathogenesis of the disease, but the treatment given is able to help the patient to reduce the pain, duration of lesion, frequency of recurrence and fasten the healing so that they can take their meals without pain and maintain the daily nutritional intake. Hence, this can improve their quality of life.

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