

Risk Factors for Recurrent Aphthous Stomatitis among College Students in Indonesia

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Abstract

Recurrent aphthous stomatitis(RAS) is a recurrent inflammatory condition of the oral mucosa. Previous research has shown that RAS often occurs in the second and third decades of life and it is known that the college student group has the most RAS. The risk factors for RAS, especially among college students in Indonesia, have not been thoroughly documented, so this study aims to present data on the risk factors for RAS among college students in Indonesia.

This study uses a rapid review method guided by the Preferred Reporting Items for Systematic Review and Meta-analysis(PRISMA) and the Population, Intervention, Comparison, Outcome(PICO) framework. Article searches using keywords and inclusion criteria through ResearchGate and Google Scholar. A total of seven articles met the criteria for review with a cross-sectional and case-control study design. Stress factors were found in all studies, local trauma and genetic in three studies, allergies and hormonal imbalance in two studies, and socioeconomic status, use of toothpaste containing detergent, frequency of brushing teeth, and water consumption were found in one study.

This study shows that socioeconomic status, genetics, allergies, hormonal imbalance, use of toothpaste containing detergents, and water consumption can be risk factors for RAS among college students in Indonesia.

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Introduction

Recurrent aphthous stomatitis (RAS) is an inflammatory condition that often occurs in the oral mucosa characterized by chronic ulcers that occur repeatedly, are round, and painful with a yellowish-gray pseudomembrane in the center surrounded by a red border (halo erythema).^{1,2} RAS affects about 20% of the general population.³ In the study of Zakiawati, et al., it was found that the highest case of oral ulceration was SAR.⁴ The etiology of RAS is still unknown with certainty⁵, but there are several risk factors that may cause RAS, such as genetic factors, local trauma, hematinic deficiency, psychological stress, allergies, hormonal factors, and smoking cessation.⁶

The prevalence of RAS in the population in the United States is around 40% and is more common in the second decade of life.⁷ In a study conducted by Mustafa Gheni Taher on the population in Diyala, it was found that the highest prevalence of RAS occurred at the age of 20-29 years, which was 46.3%.⁸ The second highest prevalence of RAS occurs at 30-39 years, which is 30%.⁸ Based on research conducted by Yojari et al., it was found that the prevalence of RAS was usually low in the first decade, then increased in the second and third decades. After the third decade, the prevalence of RAS decreases.⁹ A person with an age span of the second and third decades of life is usually a college student.

College students are people who study at a college or university.¹⁰ During the transition from high school to university, many students fail to adapt to their new environment and this causes many college students to experience stress.¹¹ In addition, women aged 18-29 years, in general have experienced menstruation, this is related to hormonal factors in the luteal phase of

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the menstrual cycle.¹² Stress and hormonal imbalance are risk factors that can cause RAS in college students.⁶

There have been several studies on risk factors for RAS in college students that have been conducted abroad, one of which was conducted in Saudi Arabia, it was found that the risk factors for RAS were decreased levels of vitamin B12, trauma, smoking cessation, stress, allergies, and the menstrual cycle.¹³ Research was also conducted in China and it was found that genetic factors, time of brushing teeth, time of exercise, and level of anxiety were factors related to RAS.¹⁴

The risk factors for RAS in college students in Indonesia are still not fully documented, there are only local data at an institution. Based on this description, this study was conducted to present data on the risk factors for RAS in students in Indonesia with an age range of 17-40 years according to the age group that often experiences RAS. This study is expected to provide knowledge about risk factors for RAS among college students in Indonesia.

Materials and methods

This study used a rapid review method conducted by PRISMA guidelines.¹⁵ Research topics are determined through research questions guided by the population, intervention, comparison, and outcome (PICO) framework.¹⁶ The sample in this study were articles with inclusion criteria in the form of accessible full-text research articles discussing risk factors for recurrent aphthous stomatitis among college students in Indonesia, articles in English and Indonesian, published in 2012-2022 (last ten years), and articles in reputable journals or with ISSN that are not included in the list of predatory journals. The research instruments used in this study were a laptop, search engines (ResearchGate and Google Scholar), Microsoft software, and Mendeley.

The articles in this study were obtained by searching through the ResearchGate, Google Scholar, and manually searching. The search for published articles in this study uses a boolean operator that combines the words "OR" and "AND" in the electronic database and the limit function of each available database. The keywords used to search the articles were (((recurrent aphthous ulceration) OR (recurrent

aphthous stomatitis)) AND ((college student) OR (university student)) AND (Indonesia)). This research was conducted from January to May 2022. Data extraction was carried out by taking data from each article. The data taken include the author's name, year of publication, title, study design, type of observational study, data collection method, research location, education, age, number of research samples, number of research samples based on gender, RAS risk factors, RAS group, control group, p-value, conclusion, percentage of RAS group and control group, and number of samples of RAS group and control group.

Results

The search for articles in this study used the PRISMA 2020 flowchart. A total of 577 articles were obtained through searches in the Google Scholar, Researchgate, and manually searching. Furthermore, the articles were screened in the first, second, and third stages to obtain as many as 20 articles. Then the article was assessed for eligibility so that seven reports were obtained to be studied. The flow chart of the search and article selection process can be seen in Figure 2.

Table 1 summarizes the general characteristics of the articles that meet the inclusion criteria. The articles were published from 2013 to 2021 with a cross-sectional and case-control observational study design.¹⁷⁻²³ The study was conducted in Manado^{17,18,20}, Makassar²¹, Pontianak¹⁹, Yogyakarta²², and Jakarta²³. Data collection was carried out using questionnaires^{17-19,21} and clinical examination^{20,22,23}.

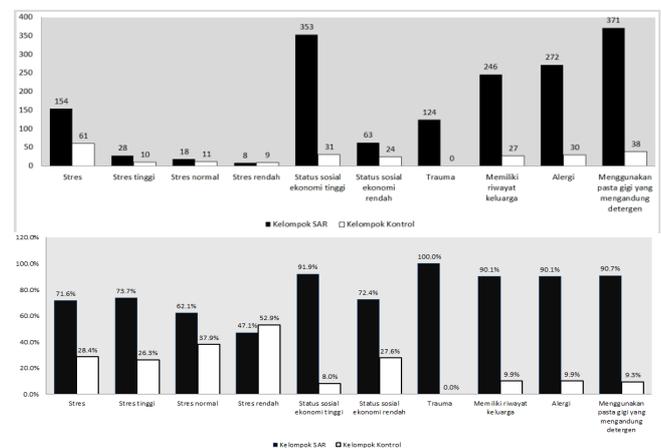


Figure 1. Number and Percentage of RAS Group and Control Group based on RAS Risk Factors.

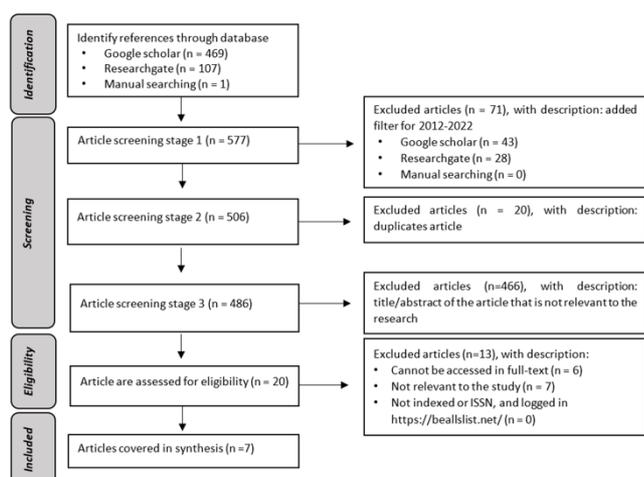


Figure 1. PRISMA Flowchart.

Table 2 overview of the research sample summary. Research subjects were divided into medical and non-medical student samples.¹⁷⁻²³ The age of the sample ranged from 17 to 40 years, with the number of research subjects from 32 to 471 people.¹⁷⁻²³ Three articles have a control group^{20,21,23} and four articles that don't have a control group.^{17-19,22}

Table 3 shows the risk factors for RAS among college students in Indonesia. These factors consist of stress factor¹⁷⁻²³ with p-value 0.000²⁰; 0.047²³; 0.315¹⁹; 0.600²¹, socioeconomic status factor with p-value 0.002²¹, local trauma factor^{17,19,21} with p-value 0.002¹⁹ and 0.143²¹, genetic factor^{17,19,21} with p-value 0.001²¹ and 0.002¹⁹, allergy factor^{17,21} with p-value 0.001²¹, hormonal imbalance factor^{17,22}, toothpaste use factor with p-value 0.000.²¹, tooth brushing frequency factor with p-value 0.305.¹⁹, water consumption factor with p-value 0.024.¹⁹

Table 4 shows the number and percentage of RAS risk factors among college students in Indonesia. The number of college students who are experiencing or have a history of RAS with stress risk factors is 154 students (71.6%)^{20,21,23}, with high-stress risk factors are 28 students (73.7%)^{20,23}, with moderate stress risk factors are 18 students (62.1 %)²⁰, with low-stress risk factors were eight students (47.1%)^{20,23}, with high socioeconomic status risk factors were 353 students (91.9%)²¹, with low socioeconomic status risk factors were 63 students (72.4%)²¹, with a local trauma risk factor of 124 students (100%)²¹, with a risk factor of having a family history of 246 students (90.1%)²¹, with an allergy risk factor of 272 students (90.1%)²¹, and with a risk factor of using

toothpaste containing detergent was 371 students (90.7%).²¹

Discussion

Based on the data in table 1, it is known that the cross-sectional research method is the most widely used because this method is relatively fast to do, does not require high costs, and can reach a large number of samples.^{17-21,23,24} Most research was conducted in North Sulawesi, the fourth province with the most dental and oral problems in Indonesia.^{17,18,20,25} The number of residents of North Sulawesi who have received dental and oral health services is still low and below the Indonesian average (10.2%).²⁵

Stress is one of the risk factors for RAS that has been studied the most because many Indonesian college students often experience stress due to academic activities.^{26,27} Two articles report a significant relationship between stress and the occurrence of RAS^{20,23} and two other articles report no significant relationship between stress and the incidence of RAS^{19,21}. This can be influenced by several factors, such as differences in education in the research sample, the different problems faced by each research subject where final year college students who are working on their final project will have different stress levels from college students who are not working on the final project, different ways of doing stress assessments, and some college students choose other risk factors, besides stress.^{19-21,23} Al-qarni et al. and Dhopte et al. found that stress had a significant relationship with the incidence of RAS.^{12,30} Stress can increase cortisol levels and cause an increase in pro-inflammatory cytokines so that there will be an imbalance of pro-inflammatory and anti-inflammatory cytokines that can make a person susceptible to RAS.^{31,32} Pro-inflammatory cytokines consist of IL-2, IL-6, IL-8, IL-12, and IL-18, while anti-inflammatory cytokines consist of IL-10.³³ In other studies, some researchers argue that stress and anxiety can cause oral parafunctional habits, such as biting lips and cheeks, which will trigger ulceration in susceptible individuals.³⁴

The socioeconomic status factor was found in one study. It was reported that the sample with the highest incidence of RAS was the sample with high socioeconomic status.²¹ This study is in line with the research of Scully et

al., which states that socioeconomic status can be a risk factor for RAS.³⁵ The highest prevalence of RAS occurs in groups with high socioeconomic status because parents with high socioeconomic status will encourage their children to be able to give the best test scores so as not to damage the family's good name.^{36,37} This is related to the occurrence of stress and causes a person to be susceptible to RAS.³⁶

Local trauma factors were found in three studies^{17,19,21}, one of which reported that local trauma had a significant relationship with the incidence of RAS²¹ and the other article reported that local trauma had no significant association.¹⁹

This is because there are students who choose risk factors other than trauma and the questionnaire questions given are specific about local trauma due to biting and brushing teeth that are too hard.¹⁹ In the study of Rajendran, local trauma was reported as a risk factor for RAS by 75% and occurred when accidentally bitten or brushing teeth too hard.³⁸ In most patients with RAS, lesions appear on the oral mucosa immediately after local trauma to the area.²⁸ Local trauma causes edema and cellular inflammation associated with increased oral submucosal extracellular matrix viscosity. This causes epithelial damage and ulcer formation.³⁹ Ulcers that are formed can also cause an unbalanced diet due to disruption of the masticatory process, resulting in atrophy of the oral mucosa and a person being susceptible to RAS.⁴⁰

Genetic factors were found in three studies and reported as a risk factor for RAS.^{17,19,21} This research is in line with the study conducted by Slebioda et al., which stated that genetics could be a risk factor for RAS.⁴¹ Most of the samples started having RAS as a child and their parents had a history of RAS.²¹ Genetic risk factors will change an individual's susceptibility to RAS associated with changes in cytokine metabolism, such as interleukins (IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-10, IL-12), interferon-gamma (IFN)- γ , and tumor necrosis factor (TNF)- α .^{3,42,36} RAS has developed towards an epigenetic mechanism so that RAS can not only be caused by genetic factors, but RAS is also heavily influenced by environmental factors, such as changes in diet that cause hematinic deficiency or allergies.⁴³

Food allergy factors were found in two studies and reported as a risk factor for RAS.^{17,21}

This study's results align with the study conducted by Slebioda et al. that allergy can be one of the risk factors for RAS.³⁶ Several foods such as chocolate, cow's milk, coffee, nuts, strawberries, cheese, potatoes, tomatoes, and wheat flour (containing gluten) influence the occurrence of RAS.⁴⁴ These foods can induce proinflammatory cytokines in RAS, making a person susceptible to RAS.³⁶ RAS caused by allergies can be detected by measuring serum IL-6.^{45,46} In one study, it was found that there was a clinical improvement after eliminating these foods.³⁶

The factor of using toothpaste containing detergent was found in one study and was reported as a risk factor for RAS.²¹ This research is in line with the study by Akintoye et al., which stated that using toothpaste containing detergent can be a risk factor for RAS.³⁹ The type of detergent in the toothpaste usually is the type of sodium lauryl sulfate (SLS).^{21,47} SLS can erode the oral mucin layer and expose the underlying epithelium, making a person more susceptible to RAS.³⁹ In another study conducted by Shim et al., it was found that using SLS can delay the healing process of ulcerations.⁴⁸

This study shows that RAS is more common in women than men.¹⁷⁻²¹ This study is in accordance with research conducted by Safely et al., which stated that RAS mostly occurred in women compared to men.⁴⁹ This is related to hormonal imbalances that women often experience during menstruation.^{18,21} Hormonal imbalance factors were found in two studies and reported as a risk factor for RAS.^{17,22} In a study by Maheswaran et al., it was found that women often experience RAS in the luteal phase of the menstrual cycle.⁵⁰ At the end of the menstrual cycle, levels of the hormones progesterone and estrogen decrease.⁵¹ Decreased estrogen levels can cause a decrease in blood flow, thinning of the epithelium, slowing the process of keratinization of the oral mucosa, especially in the mouth, so that it can cause inflammation and the occurrence of RAS.^{49,52} Low levels of progesterone can decrease anti-inflammatory function.⁵² As a result, the oral mucosa becomes vulnerable and inflammation that can cause RAS is easy occurs.⁵²

The factor of lack of water consumption was found in one article and it was reported that there was a significant relationship with the incidence of RAS.¹⁹ In a study by Xu et al., it was

found that adequate drinking water consumption can prevent RAS.⁵³ Lack of water consumption can cause hyposalivation.⁵⁴ Hyposalivation can reduce the protection of the oral mucosa so that a person will be susceptible to RAS.⁵⁵ In addition, drinking water contains several mineral contents, such as iron, calcium, and zinc.⁵⁶ Iron content plays a role in oxygen transportation, so when there is iron deficiency, there will be hypoxia of oral mucosal tissue, which causes atrophy of the oral mucosal epithelium.⁵⁷ Lack of calcium can cause a decrease in tissue polarity so that the integrity of the oral mucosa is disrupted.⁵³ Lack of zinc levels causes cytokine production to be disrupted so that a person will be more susceptible to RAS.⁵⁸ RAS is also known to be more common in someone who has zinc deficiency.^{59,60}

The factor of tooth brushing frequency that did not meet the requirements was discussed in one article and reported that there was no significant relationship with the incidence of RAS.¹⁹ The frequency factor of brushing teeth that does not meet the requirements has a 21.43% possibility of causing RAS.¹⁹ The frequency of brushing teeth is related to oral hygiene, which can reduce the number of bacterial colonies in the oral cavity.¹⁹ Several bacteria are suggested to have a relationship with the incidence of RAS, one of which is *Streptococcus sanguinis*.³⁶ *Streptococcus sanguinis* acts as a stimulant antigen that cross-reacts with oral keratinocytes' mitochondrial heat shock protein. This reaction can induce a T-cell-mediated immune response that causes damage to the oral mucosa. However, other studies state that the response of lymphocyte proliferation to *Streptococcus sanguinis* in RAS patients is not significantly different from the control group.⁶¹ Another bacterium is *Helicobacter pylori*. In one

study, after eradication of *Helicobacter pylori*, a positive correlation was found with increase in vitamin B12 levels and decreased in lesions.³⁹ In another study conducted to identify *Helicobacter pylori* in RAS patients, no significant association was found between RAS and *Helicobacter pylori*.³⁹ Therefore, until now, there is no conclusive data linking RAS with a specific microorganisms.⁶²

This rapid review study has limitations that need to be considered, namely using only two databases. Further research on drinking water consumption factors can be considered because there is still minimal information on this matter.

Conclusions

Risk factors for RAS among college students in Indonesia consist of socioeconomic status, genetics, allergies, hormonal imbalance, use of toothpaste containing detergent, and consumption of water.

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No.	Author's name	Year of Publication	Title	Study Design	Type of Observational Study	Method of Collecting Data	Location
1	Suling et al.	2013	Angka Kejadian Lesi yang Diduga Sebagai Stomatitis Aftosa Rekuren pada Mahasiswa Program Studi Kedokteran Gigi Fakultas Kedokteran Universitas Sam Ratulangi	Observational Study	Descriptive cross-sectional	Questionnaire	Manado, North Sulawesi
2	Tangkilisan et al.	2013	Gambaran Stres pada Mahasiswa Pendidikan Profesi Program Studi Kedokteran Gigi Fakultas Kedokteran Universitas Sam Ratulangi yang Memiliki Pengalaman Stomatitis Aftosa Rekuren	Observational Study	Descriptive cross-sectional	Questionnaire	Manado, North Sulawesi
3	Widyastutik et al.	2017	Faktor yang Berhubungan dengan Stomatitis Aftosa Rekuren pada Mahasiswa di Pontianak	Observational Study	Analytical cross-sectional	Questionnaire	Pontianak, West Kalimantan
4	Wowor et al.	2019	Hubungan Stres dengan Stomatitis Aftosa Rekuren pada Mahasiswa Program Studi Pendidikan Dokter Gigi Universitas Sam Ratulangi	Observational Study	Analytical cross-sectional	Clinical examination	Manado, North Sulawesi
5	Masriadi	2019	Epidemiologi Stomatitis Aftosa Rekuren pada Mahasiswa Universitas Indonesia Timur Makassar	Observational Study	Analytical cross-sectional	Questionnaire	Makassar, South Sulawesi
6	Susanto et al.	2019	Decreased Salivary Cortisol in Recurrent Aphthous Stomatitis Treated with Topical Steroids	Observational Study	Analytical case-control	Clinical examination	Yogyakarta
7	Purnama et al.	2021	Academic Stress on the Incidence of Recurrent Aphthous Stomatitis: A Cross Sectional Study	Observational Study	Analytical cross-sectional	Clinical examination	Jakarta

Table 1. General Study Characteristics.

No.	Author's name	Education		Age		Number of Study Samples	Gender		Control Group	SAR Group Gender	
		Medical	Non-medical	Min	Max		Male	Female		Male	Female
1	Suling et al.	Yes	-	22 years	26 years	66 people	18 people	48 people	-	14 people	31 people
2	Tangkilisan et al.	Yes	-	18 years	29 years	62 people	17 people	45 people	-	17 people	45 people
3	Widyastutik et al.	Yes	Yes	18 years	28 years	279 people	81 people	198 people	-	81 people	198 people
4	Wowor et al.	Yes	-	18 years	22 years	64 people	16 people	48 people	√	8 people	23 people
5	Masriadi	Yes	-	17 years	40 years	471 people	131 people	340 people	√	110 people	306 people
6	Susanto et al.	Yes	Yes	18 years	30 years	32 people	0	32 people	-	N/A	32 people
7	Purnama et al.	Yes	-	20 years	22 years	36 people	2 persons	34 people	√	N/A	N/A

Table 2. Characteristics of Research Sample.

RAS risk factors	RAS Group		Control Group		Total n
	n	%	n	%	
Stress	154	72	61	28	215
High stress	28	73.7	10	26.3	38
Moderate stress	18	62.1	11	37.9	29
Low stress	8	47.1	9	52.9	17
High socioeconomic status	353	91.9	31	8.1	384
Low socioeconomic status	63	72.4	24	27.6	87
Local trauma	124	100	0	0	124
Genetic	246	90	27	10	273
Allergy	272	90	30	10	302
Using toothpaste that contains detergent	371	90.7	38	9.3	409

Table 3. Risk Factors for RAS among College Students in Indonesia.

No.	Author's name	RAS risk factors	RAS Group	Control Group	P-value	Conclusion
1	Suling et al.	Trauma	41	N/A	N/A	N/A
		Not traumatized	4	N/A	N/A	N/A
		Hormonal imbalance	9	N/A	N/A	N/A
		No hormonal imbalance	36	N/A	N/A	N/A
		Genetics	11	N/A	N/A	N/A
		No genetics	34	N/A	N/A	N/A
		Stress	15	N/A	N/A	N/A
		No stress	30	N/A	N/A	N/A
		Allergy	1	N/A	N/A	N/A
		Not allergic	44	N/A	N/A	N/A
2	Tangkilisan et al.	High stress	37	N/A	N/A	N/A
		Normal stress	20	N/A	N/A	N/A
		Low stress	5	N/A	N/A	N/A
3	Widyastutik et al.	Genetic	N/A	N/A	0,002	There is a significant relationship between genetics and RAS
		No genetics	N/A	N/A		
		Toothbrush trauma	N/A	N/A	0,002	There is a significant relationship between trauma and RAS
		No tooth brushing trauma	N/A	N/A		
		Not enough water consumption	N/A	N/A	0,024	There is a significant relationship between water consumption and RAS
		Just drink water	N/A	N/A		
		Does not meet the requirements for toothbrush frequency	N/A	N/A	0,305	There is no significant relationship between toothbrush frequency and RAS
		Meet the requirements for the frequency of toothbrushes	N/A	N/A	0,315	There is no significant relationship between stress and RAS
4	Wowor et al.	High stress	13	6	0	There is a significant relationship between stress and RAS
		Moderate stress	18	11		
		Low stress	0	16		
5	Masriadi	High socioeconomic status	353	31	0,002	There is a significant relationship between socioeconomic status and RAS
		Low socioeconomic status	63	24		
		Experiencing trauma	124	0	0,143	There is no significant relationship between trauma and RAS
		No trauma	292	55		
		Have a family history	246	27	0,001	There is a significant relationship between family history and RAS
		No family history	170	28		
		Have allergies	272	30	0,001	There is a significant relationship between allergy and RAS
		Have no allergies	144	25		
		Stress	100	15	0,6	There is no significant relationship between stress and RAS
		No stress	316	40		
Using foaming toothpaste	371	38				
Do not use foaming toothpaste	45	17	0	There is a significant relationship between the use of foamed toothpaste and RAS		
6	Susanto et al.	Stress	11	N/A	N/A	N/A
		Hormonal factors	6	N/A	N/A	N/A
		Stress and hormonal factors	14	N/A	N/A	N/A
		Unknown	1	N/A	N/A	N/A
7	Purnama et al.	High stress	15	4	0,047	There is a significant relationship between stress and RAS
		Low stress	8	9		

Table 4. Percentage of RAS Risk Factors among College Students in Indonesia.

Declaration of Interest

The authors report no conflict of interest.

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