

Characteristics of Anosmia Cases in Covid-19 Patients: a Systematic Review

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Abstract

Introduction: Anosmia is one of the clinical neurological manifestations in Covid-19 patients and is an important clue in the diagnosis of Covid-19. These symptoms can occur in the early stages of Covid-19 disease. The characteristics of anosmia in covid-19 patients are not widely known, therefore a study is needed to be able to understand the overall picture of Covid-19 patients with anosmia symptoms. This information can be used as a screening and diagnosis of Covid-19 in order to get immediate treatment, so that the cure rate increases

Purpose: to determine the characteristics of anosmia cases in COVID-19 patients

Methodology: This study used database sources from the Pubmed and Science Direct, using keywords (“severe acute respiratory syndrome coronavirus 2” OR “severe acute respiratory syndrome coronavirus 2” OR “ncov” OR “2019-nCoV” OR “COVID-19” OR “SARS-CoV-2”) AND (“olfaction disorders” OR Anosmia). This research had an ethical clearance provision from Ethical Clearance Committee FK UMS No 3096./C.1/KEPK-FKUMS/XI /2020.

Results: the mean age of anosmia was 47.5 years and was more prevalent in women. The average full recovery time was 21 days, the most comorbid in cases of anosmia was hypertension, and nasal congestion was the most comorbid nasal symptom in cases of anosmia.

Conclusion: Based on characteristic age, sex, symptoms of anosmia, nasal congestion in young women with various comorbidities, and especially hypertension, can be considered for screening cases of Covid-19.

Applications/Originality/Value: This research can be used as information to the public about the characteristics of anosmia and can find out the factors that can affect someone infected with Covid-19. Previous publications on anosmia have not fully discussed the characteristics of anosmia, but in this study the characteristics of anosmia are quite completely discussed.

Introduction Section

In the end of 2019, on 31 of December, the Coronavirus Disease 2019 (COVID-19) outbreak occurred in Wuhan, and spread rapidly throughout the world (Meng et al., 2020). Clinical evidence has shown that the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be transmitted from person to person (Meng et al., 2020). Early March 2020, Indonesia had reported 2 confirmed cases of Covid-19. The increase in the number of cases took place quite rapidly and has spread throughout the province. The last update on September 16, 2020, confirmed cases of Covid-19 were 228,993. The percentage of deaths in Indonesia is much higher than that of the People’s Republic of China (8.9% vs 4%) (Tosephu et al., 2020).

In May 2020, anosmia or loss of smell is recognized as a symptom of Covid-19, which has a severe and sudden onset. Interestingly, this patient can experience sudden anosmia without other symptoms such as nasal obstruction, rhinitis and others (Luigi A., 2020). In a retrospective study, 54 (47%) of 114 confirmed Covid-19 patients had anosmia (Meng et al., 2020), 19 patients (83%) reported an early symptom of Covid-19 and anosmia could be the only clinical presentation. Covid-19 without other significant symptoms (Heidari et al., 2020). In a meta-analysis study showed a loss of smell of 55% and 10.6% of patients showed no improvement within one month (Walker et al., 2020).

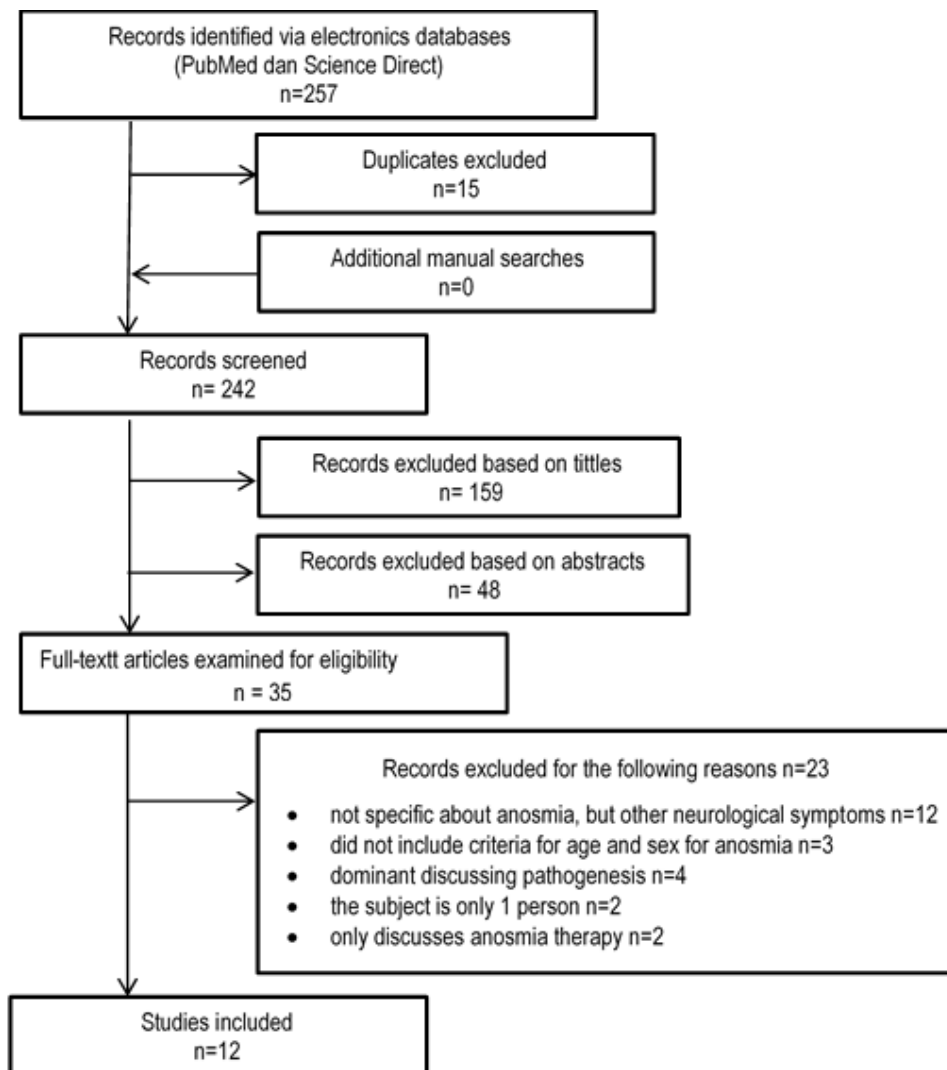
Anosmia is one of the clinical neurological manifestations in Covid-19 patients and an important clue for the diagnosis of Covid-19, this symptom can occur in the early stages of the disease. The characteristics of anosmia in Covid-19 patients are not widely known, therefore a study is needed to understand the overall picture of Covid-19 patients with anosmia symptoms (Lee et al., 2020). This information can be used as a screening and diagnosis of Covid-19 in order to get immediate treatment, so that the cure rate increases (Heidari et al., 2020).

Methodology

This systematic review was prepared by adjusting the PRISMA guidelines, takes research sources from various countries and races with the limitation of the search time limit is 2020. The e-databases were PubMed and Science Direct using keywords: (“severe acute respiratory syndrome coronavirus 2” OR “severe acute respiratory syndrome coronavirus 2 “OR” nCoV “OR” 2019-nCoV “OR” COVID-19 “OR” SARS-CoV-2 “) AND (“olfaction disorders “OR Anosmia). The eligibility criteria of the articles that were synthesized were as follows: English literature, all age and gender categories, all countries and races, quantitative research, empirical research.

The search results on the PubMed web in 2020 were 81. The search results on the Science Direct web in 2020 amounted to 176, so that the database was 257 literatures, after that removed duplicates using Ms. Excel and obtained 15 multiple journals on the two websites. The results of remove duplicates left 242 journals, and then a screening stage was carried out based on the title and obtained 159 titles that did not match the title of this study, then a screening was carried out based on the abstract and obtained 48 journals that did not match the research theme, so that there were 35 journals left. The last stage is screening by reading the journal’s full text, there are 12 that fit the inclusion criteria. Flowchart can be seen in [Figure 1](#).

Twenty three journals were excluded because: (1) not specific about anosmia, but other neurological symptoms n=12, (2) did not include criteria for age and sex for anosmia n=3 (3) dominant discussing pathogenesis n=4 the subject is only 1 person n=2, (4) only discusses anosmia therapy n=2.



[Figure 1](#) Flowchart Prisma.

Result

Table 1. Based on the characteristics of age, gender, and comorbidities

No.	Study design	Sample size (n)	Sex (n,%) and Age (y.o)	Comorbid (n, %)
1.	Prospective cohort	29	Male (18, 63%); Female (11, 37%) average age = 63	Does not include any comorbid factors
2.	Retrospective cohort	54	Male (18, 33%); Female (36, 67%) average age = 47	Arterial hypertension 7 (13%) Cardiovascular disease 6 (11%) Diabetes mellitus 2 (4%) Asthma 7 (13%) COPD 0 (0%) Malignancy 2 (4%) Immunosuppression 1 (4%)
3.	Case series	345	Male (146, 42%); Female(199, 57%) average age = 50	Does not include any comorbid factors
4.	Prospective cohort	202	Male (97, 48%); Female(105, 51%) average age = 56	comorbid 113 (55.9%), does not include comorbid diseases
5.	Prospective cohort	15	No mention about gender average age = 40	Comorbid 6 (9.5%) does not include comorbid diseases.
6.	Prospective cohort	96	Male (40, 42%); Female (56, 58%) average age = 50	Diabetes mellitus (16%) Hypertension (8%)
7.	Prospective cohort	126	No mention about gender average age = 50	Diabetes mellitus (16%) Hypertension (8%) Allergic rhinitis (25%)
8.	Prospective cohort	417	Male (54 (36%) Female (263,63%) average age = 56	Does not include any comorbid factors
9.	Prospective cohort	237	Male (108, 45%) Female (129, 54%)	Does not include any comorbid factors
10.	Prospective cohort	448	Male (152, 33%); Female (336,75%) average age = 39,6	Does not include any comorbid factors
11.	Case series	41	Male (15, 36%); Female (36, 87%) average age =40	Hypertension (0) Allergic rhinitis (1) Reflux (4) Asthma (2)

12.	Prospective cohort	51	Male (15, 29%); Female (36, 71%) Average age =42	Does not include any comorbid factors
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Table 2. Based on the characteristics of onset anosmia, Severity, nasal symptoms, full recovery of anosmia

No.	Onset of anosmia	Severity	Nasal Symptoms	Full Recovery of anosmia
1.	The first symptom or attack	-	Not accompanied by previous nasal symptoms	Average = 28 days
2.	Anosmia was confirmed after being diagnosed with Covid-19	-	Nasal obstructions 16 (30%) Cough 47 (87%)	Average = 28 days
3.	Day 2 after being diagnosed with Covid-19	Asimptomatic, Mild, Moderate, dan Severe,	Not accompanied by previous nasal symptoms	Average = 30 days
4.	The first symptom or attack	Very mild, Mild, Moderate, dan Severe	Dry cough or coughing up mucus 122 (60.4%) Sinonasal pain 35 (17.3%)	Average = -
5.	Day 3 after being diagnosed with Covid-19	Mild	Not accompanied by previous nasal symptoms	Average = 17 days
6.	As the first symptom or attack a number of 80 and the onset of anosmia symptoms after diagnosis 16	-	Not accompanied by previous nasal symptoms	Average = 17 days
7.	The first symptom or attack	-	Nasal obstruction 40 Sneezing 18 Coryza 31 Rhinorrhea 2 Nasal pruritus 6	Average = 17 days
8.	The first symptom or attack	-	Cough 15 (44%) Rhinitis 8 (24%)	Average = 15 days
9.	as the first symptom or attack a number of 176 and the onset of anosmia symptoms after diagnosis 65	-	Cough 98 (41%) Nasal congestion 60 (25 %) Rhinorrhea 42 (18%)	Average = -
	The first symptom or attack	-	Not accompanied by previous nasal symptoms	Average = 15 days
11.	The first symptom or attack	Mild	Nasal obstruction 13	Average = 17 days
12.	The first symptom or attack	-	Not accompanied by previous nasal symptoms	Average = 21 days

Discussion

Characteristics of anosmia symptoms in Covid-19 patients based on age and sex according to a study conducted by Meini et al. 63 years, for the male gender, there are 18 people (Meini et al., 2020). Research conducted by Klopfenstein, et al., A study conducted directly on patients with anosmia $n = 54$, obtained an average age of 47 years, with the female sex being more dominant, namely 36 (Klopfenstein et al., 2020). A prospective cohort design study conducted by Vaira et al., With an anosmia patient population of 345, obtained an average age of 50 years and the number of women who experienced anosmia was 199 (Vaira et al., 2020). According to a study conducted by Chiesa-Estomba et al. with a population of 417 anosmia patients, the average age was 56 years and more women were 263 (Chiesa-Estomba et al., 2020).

The Prospective Cohort design study conducted by Amer et al. with an anosmia population of 96 with an average age of 50 years, and in this study the more experiencing anosmia were women, namely 56 (Amer et al., 2020). The study conducted by Spinato et.al found anosmia population of 202 with an average age of 56 years, in this study it was also dominated by women, namely 105 anosmia patients (Spinato et al., 2020). According to a study by Kosugi et al., with a population of 126 anosmia patients, the average age of anosmia patients was 50 years, but in this study, the gender demographics were not stated (Kosugi et al., 2020). The study conducted by Levinson et.al with anosmia number of 15 from 45 Covid-19 patients did not include gender demographic data, for the mean age was 40 years (Levinson et al., 2020).

Research conducted by Kaye et al. with a retrospective cohort study found an average age of 39.6 years, the presentation of gender in this study was more dominant in women (Kaye et al., 2020). Research conducted by Lee et.al with a population of Covid-19 patients, 703 found 448 anosmia patients, with an average age of 36.5 years, more women experienced anosmia than men, namely 336 (Lee et al., 2020). A study conducted by Leichen et al. with the number of Covid-19 patients was 86 and found 41 anosmia patients, with an average age of 41 years, for the predominant female gender, namely 36 (Leichen et al., 2020). Meanwhile, the research conducted by Hopkin et al., with a population of Covid-19 and anosmia 51 and an average age of 42 years. The female gender is more than 36 (Hopkins et al., 2020).

Based on the description of some of the literature above, there are 9 journals with the results of women's research that dominate anosmia patients in Covid-19. Age characteristics based on 12 literatures were calculated by means of the formula a mean of 47.5 years. The literature study states that anosmia predominantly occurs in women and is younger, but the mechanism of its occurrence has not been further studied (Klopfenstein, et al, 2020) [Table 1](#).

The characteristics of comorbid anosmia in Covid-19 patients varied. Research conducted by Klopfen et al. states that some comorbid anosmia are arterial hypertension 7 (13%), cardiovascular disease 6 (11%), diabetes 2 (4%), asthma 7 (13%), chronic obstructive pulmonary disease 0 (0%)., malignancy 2 (4%) immunosuppression 1 (4%). Amer et al. study on diabetes mellitus (16%) and hypertension (8%). Based on research by Kosugi et al. mentioned diabetes mellitus (16%), hypertension (8%), allergic rhinitis (25%) are comorbid anosmia. Leichen et al.'s study found comorbid hypertension 0, rhinitis 1, reflux 4, and asthma 2. Research by Levinson et al. and Amer et al. found comorbidities but did not mention any comorbid. There are 6 literatures that do not mention any comorbid factors, namely Meini et al., Vaira et al., Chiesa-Estomba et al., Kaye et al., Hopkin et al., and Lee et al.

Literature studies have not yet discussed why these comorbid can accompany anosmia patients, but a study conducted by Klopfen et al. stated that anosmic patients have a low comorbid rate in young adults and are not closely related to the incidence of anosmia (Levinson et al., 2020). Based on the comorbid above, the highest percentage is hypertension.

The characteristics of the recovery time of anosmia patients, based on the study conducted by Meini et al. and Klopfenstein, et al. The average healing time was 28 days. The average healing time of 17 days is the result of studies by Amer et al., Kosugi et al., Levinson, et al. and Leichen et al. The results of the research conducted by Vaira et al. were 30 days. Research conducted by Lee. et al. was 20.5 days, and according to the Hopkin et al. study it was 21 days and for Chiesa-Estomba et al.'s study it was only 15 days. The average of 10 journals found 21 days or 3 weeks of anosmia recovery time in Covid-19 patients. The age group over 20-39 years, shows a tendency to be associated with a longer recovery of anosmia (Lee. et al. 2020).

The characteristics of anosmia in Covid-19 patients based on nasal symptoms varied. There are 6 literature states that anosmia is not accompanied by previous nasal symptoms. According to research conducted by Klopfen et al., nasal symptoms that occur before anosmia are nasal obstruction 16 (30%) and cough 47 (87%). Meanwhile, according to Spinato et al., it is dry cough or coughing up mucus 122 (60.4%) and sinonasal pain 35 (17.3%). The results of the Chiesa-Estomba et al. study showed that previous nasal symptoms were Cough 15 (44%) and Rhinitis 8 (24%).

Based on research by Kosugi et al., there are nasal obstruction 40, sneezing 18, coryza 31, rhinorrhea 2 and Nasal pruritic 6 as previous nasal symptoms. Meanwhile, according to a study conducted by Kaye et.al, it was cough 98 (4 1%), nasal congestion 60 (25%), and rhinorrhea 42 (18%). The last one is a study from Leichen et al. is nasal obstruction 13. The mechanism of nasal symptoms that accompany anosmia patients is not due to post-viral infection from Covid-19, but the mechanism of inflammation and nasal obstruction preventing odor molecules from entering the olfactory nerves (Levinson et al., 2020). Nasal obstruction is the symptom with the greatest percentage. Table 20.

Conclusion

Based on age characteristics and calculated by means of the formula obtained 47.5 years, and dominant in women. Based on varied comorbid characteristics and hypertension has the largest presentation. Nasal congestion is a characteristic of the nasal symptoms accompanying anosmia in the largest percentage. This information can be used for early detection of Covid-19.

References

- Allameh, S., Saffapour, R., & A., N. (2020). All about COVID-19 in brief. *New Microb and New Infect*, 35 number C, 1-3.
- Amer, M. A., Elsherif, H. S., Abdel-Hamid, S. A., & Elzayat, S. (2020). Early recovery patterns of olfactory disorders in COVID-19 patients; a clinical cohort study. *Am J Otolaryngol*, (41) 102725, 1-5.
- Basuki, S. W., & Nilawati, D. D. (2011). Pengaruh merokok terhadap faal paru. *journal Biomedik*, Vol.3 No.2, 1-8.
- Brann, D. H., Tsukahara, T., Weinrab, C., & Lipovsek, M. (2020). Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID19-associated anosmia. *Science Advances*(10.1126/sciadv.abc5801), 1-29.
- Burhan, E., Isbaniah, F., Susanto, A. D., Yoga, T. A., soedarsono, Saertono, T. R., et al. (2020). *Pneumonia Covid-19 Diagnosis dan Penatalaksanaan*. Jakarta: Perhimpunan Dokter Paru Indonesia.
- Chiesa-Estomba, C. M., Leichen, J. R., & De Siati, D. R. (2020). Olfactory and Gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the Coronavirus Disease (COVID-19): A multicenter European Study. *European Archives Of Oto-Rhino-Laryngology*, Vol.277, 2251-2261.
- Equils, O., Lekaj, K., Fattani, S., Wu, A., & Liu, G. (2020). Proposed mechanism for anosmia during COVID-19: The role of local zinc distribution. *Journal of Translational Science*, Vol.7, 1-2.
- Hayati, R. (2020). *Penelitian Ilmiah.com*. Retrieved Juni 5, 2019, from <https://penelitianilmiah.com/penelitian-naratif/>
- Heidari, F., Karimi, E., & Firouzifar, M. (2020). Anosmia as a prominent symptom of COVID-19 infection. *Rhinology*, 302-303.
- Hopkins, C., Surda, P., Whitehead, E., & Kumar, B. N. (2020). Early recovery following new onset anosmia during the COVID-19 pandemic – an observational cohort study. *Journal of Otolaryngology - Head and Neck Surgery*, 49:26, 1-6.
- Huriyati, E., & Nelvia, T. (2014). Gangguan Fungsi Penghidu dan Pemeriksaannya. *Jurnal Kesehatan Andalas*, 3(1), 1-7.
- Itoh, N., Yufika, A., Winardi, W., Keam, S., Megawati, D., & Harapan, H. (2020). Coronavirus disease 2019 (COVID-19): A literature review. *Journal of Infection and Public Health*, 13, 667–673.

- Kaye, R., Chang, D., Kazahaya, K., Brereton, J., & Denny, J. (2020). COVID-19 Anosmia Reporting Tool: Initial Findings. *Otolaryngology–Head and Neck Surgery*, 1-3.
- Klopfenstein, T., Kadiane-Oussou, N., Toko, L., Lepiller, Q., & Gendrin, V. (2020). Features of anosmia in COVID-19. *Médecine et maladies infectieuses*, 1-5.
- Lechien, J. R., Chiesa-Estomba, C. M., De Siati, D. R., & Horoi, M. (2020). Olfactory and gustatory dysfunctions as a clinical presentation of mild to moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *European Archives of Oto-Rhino-Laryngology*, 1-11.
- Lee, Y., Min, P., Lee, S., & Kim, S.-W. (2020). Prevalence and Duration of Acute Loss of Smell or Taste in COVID-19 Patients. *J Korean Med Sci*, 35(18):e174, 1-6.
- Leichen, J. R., Cabaraux, P., Chiesa-Estomba, C. C.-E., Khalife, M., & Hans, S. (2020). Objective olfactory evaluation of self-reported loss of smell in a case series of 86 COVID-19 patients. *Head & Neck*, 42, 1583–1590.
- Levinson, R., Elbaz, M., Ben-Ami, R., & Levinson, T. (2020). Anosmia and dysgeusia in mild COVID-19. 1-12.
- Lotfi, M., Hamblin, M. R., & Rezaei, N. (2020). COVID-19: Transmission, prevention, and potential therapeutic. *Clinica Chimica Acta*, 508, 254-266.
- Luigi A., G. S. (2020). Anosmia and Ageusia: Common Findings in COVID-19 Patients. 1787-1787.
- Meini, S., Suardi, L. R., Busoni, M., Roberts, A. T., & Fortini, A. (2020). Olfactory and gustatory dysfunctions in 100 patients hospitalized for COVID-19: sex differences and recovery time in real life. *Journal European Archives of Oto-Rhino-Laryngology*, 1-5.
- Meini, S., Suardi, L. R., Busoni, M., Roberts, A. T., & Fortini, A. (2020). Olfactory and gustatory dysfunctions in 100 patients hospitalized for COVID-19: sex differences and recovery time in real life. *European Archives of Oto-Rhino-Laryngology*, 1-5.
- Meng, X., Deng, Y., Dai, Z., & Meng, Z. (2020). COVID-19 and anosmia: A review based on up-to-date knowledge. *Am J Otolaryngol*, 41, 1-6.
- Pascarella, G., Strumia, A., Pilego, C., Buono, R. D., & Costa, F. (2020). COVID-19 diagnosis and management: a comprehensive review. *Journal of Internal Medicine*(10.1111/joim.13091), 1-15.
- Shi, Y., Wang, G., Cai, X.-p., Deng, J.-w., Zheng, L., Zhu, H.-H., et al. (2020). An overview of COVID-19. *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)*(ISSN 1673-1581), 1-18.
- Soler, Z. M., Patel, M. Z., Turner, H. J., & Holbrook, E. H. (2020). A primer on viral-associated olfactory loss in the era of COVID-19. *International Forum of Allergy & Rhinology*, Vol. 10, No. 7, 814-820.
- Spinato, G., Fabbris, C., Polesel, D., Cazzador, D., Hopkins, C., & Boscolo-Rizzo, P. (2020). Alterations in Smell or Taste in Mildly Symptomatic Outpatients With SARS-CoV-2 Infection. *American Medical Association*, Vol. 323 No.20, 1-3.
- Thomas, D. C., & Mahalakshmi, S. (2020). Anosmia A review in the context of coronavirus disease 2019 and orofacial pain. *JADA*, 151(9), 696-702.
- Tosephu, R., Effendy, D. S., Ahmad, L. A., Lestari, H., Bahar, H., & Asfian, P. (2020). Correlation between weather and Covid-19 pandemic in. *Science of the Total Environment*, 725 (2020) 138436, 1-4.
- Vaira, L. A., Hopkins, C., & Salzano, G. (2020). Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter-study. *Head & Neck*, Vol. 42, 1560–1569.
- Vardavas, C. I., & Nikitara, K. (2020). COVID-19 and smoking: A systematic review of the evidence. *Journal of Tobacco induced Diseases*, 1-4.
- Villalba, N. L., Maoucho, Y., Sosa, Z. C., & Pertoldi, P. (2020). Anosmia and Dysgeusia in the Absence of Other Respiratory Diseases: Should COVID-19 Infection Be Considered? *European Journal of Case Reports in Internal Medicine*(10.12890/2020_001641), 1-3.
- wahono, R. S. (2020). *Romisatriawahono.net*. Retrieved Mei 17, 2016, from <https://romisatriawahono.net/2016/05/07/literature-review-pengantar-dan-metode/>.

- Walker, A., Pottinger, G., & Scotter, A. (2020). Anosmia and loss of smell in the era of covid-19. *the bmj*, 1-6.
- Whitcroft, K. L., & Hummel, T. (2020). Olfactory Dysfunction in COVID-19 Diagnosis and Management. *American Medical Association*, 323 No.24, 1-3.
- Zahra , S. A., Iddawela, S., Pillai, K., Choudhury, R. Y., & Harky, A. (2020). Can symptoms of anosmia and dysgeusia be diagnostic for COVID-19? *Brain and Behavior*, 1-18.