pISSN 2302-1381
eISSN 2338-4506

IJIHS International Journal of Integrated Health Sciences

Original Articles

Case Reports

Volume 11, Number 2, September, 2023

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Original Article

Intention to Consume Alcohol among Dayak Adolescents in Sarawak: An Application of Theory of Planned Behavior

Mohd Faiz Gahamat, Md Mizanur Rahman, Razitasham Safii, Muhammad Siddiq Daud, Rudy Ngau Ajeng

Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Kota Samarahan, Sarawak, Malaysia

Article History

Received: May 17, 2023
Accepted: September 05, 2023
Published: October 30, 2023

DOI: 10.15850/ijihs.v11n2.3353
IJIHS. 2023;11(2):63–69

Correspondence:
Md Mizanur Rahman
Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, 94300, Kota Samarahan, Sarawak, Malaysia.
Email: rmmizanur@unimas.my; aniqm@hotmail.com

Abstract

Objectives: To explore the application of a model that integrates various factors that influence Dayak adolescents' intentions to consume alcohol in Sarawak, Malaysia.

Methods: A cross-sectional quantitative study was conducted from September 2019 to February 2022. Through multistage stratified cluster sampling, 12 districts were selected from 12 divisions. Respondents were selected randomly and were interviewed using a questionnaire.

Results: Structural equation modeling was used to test the Theory of Planned Behavior (TPB) and explore the relationship between various variables and respondents' intention to consume alcohol. The findings suggest that attitude (β=.22, p<.001), subjective norm (β=33, p<.001), and perceived behavior control (β=−.41, p< .001) influenced the intention to consume alcohol. In contrast, alcohol consumption was associated with intention (β=.15, p <.001), attitude (β= .20, p<.001), and perceived behavior control (β=−.32, p<.001).

Conclusion: The findings demonstrated that the TPB model can be used to explore various variables that influence the intention to consume alcohol among Dayak adolescents, with attitude, subjective norm, and perceived behavior control as the variable influencing the intention. This highlights the need for paying attention to those variables when developing age-appropriate strategies that address various social levels to curb alcohol consumption. Given the concerning rates of risky drinking and dependency, school-based health initiatives and focused screening for Dayak adolescents are crucial.

Keywords: Adolescents, alcohol, dayak, theory of planned behavior

Introduction

Ethanol, alcohol's psychoactive component, is a molecule that contains carbon atoms and the hydroxyl (-OH) group. It is commonly referred to as ethanol or ethyl alcohol, and is known to have stimulant effects. Ethanol is produced through fermentation and distillation and is the key ingredient in various beverages, including wine, beer, and hard liquor.[1] Early alcohol use is believed to be detrimental to adolescent brain's development, particularly in those who begin drinking before or by age 15.[2] Such individuals may experience alcohol-related problems later in life, such as alcohol dependency and a consistent pattern of high alcohol use.[3] These problems can lead to physical or mental disorders as described in the Diagnostic and Statistical Manual of Mental Disorders.[4] Alcohol use disorder, or previously known as alcoholism or alcohol dependence, is characterized by an excessive alcohol consumption that causes personal or professional problems, an inability to regulate drinking, and the need for increasing the amount of alcohol consumed to achieve the same effects.[5] Alcohol consumption in Malaysia has steadily risen, increasing from 0.8 liters in 2005 to 1.7 liters in 2015 per person.[6] However, the prevalence of alcohol

usage in Malaysia is lower than in other Western Pacific nations, with only 8.0% of Malaysian adults regularly consuming alcohol. The proportion of older persons who drink has declined from 7.8% in 2006 to 4.0% in 2015.[7] It is also worth noting that the "Bumiputras" population in Malaysia has contributed to the highest percentage of alcohol consumption in 2015 with 21.6%. Furthermore, 75% of the "Bumiputras" engage in binge drinking. Although the prevalence of binge drinking has decreased since the previous survey in 2011, there has been an increase among current drinkers and adolescents.[6] Sarawak is one of the states in Malaysia with the highest percentage of current drinkers, with more than one-fifth of the population, equals to 500,000 individuals, currently consumes alcohol. Interestingly, the urban areas had a larger proportion of current drinkers than rural areas, men, and those with higher levels of education.[8]

In predicting alcohol consumption, the Theory of Planned Behavior (TPB) is one of the popular models, particularly for researching adolescents.[9,10] This model assumes behavioral intentions as the precursors to behavior rather than attitudes. Attitude, subjective norm, and perceived behavioral control influence the intention. Each of these factors has its own set of influencing factors. The attitude variable represents the perceived likely qualities of the behavior. In contrast, the subjective norm represents the perceptions of others' specific preferences on whether or not one should engage in the conduct. Perceived behavioral control is similar to the idea of self-efficacy and is the belief that a person's behavior is under their control. Implicit attitudes toward alcohol, in addition to readiness and intention to drink, which develop over time with a regular exposure to alcohol beverages, may influence risky drinking in young individuals, as stated by Davies *et al*.[11] Binge drinking was more likely to be reported by those with a positive attitude toward it and who consider the behavior as socially acceptable and manageable behavior.[10] Anti-alcohol and pro-abstinence social systems imposed by friends, family, and community are linked to greater anti-alcohol subjective norms and attitudes among teenagers, according to Zhao *et al*.[12]

Adolescent alcohol consumption is currently rising worldwide,[13] particularly in Malaysia.[14] Even though adolescents rarely drink, they consume more alcohol on each occasion than adults.[15] Identifying them as a high-risk group is critical for developing more a effective and viable intervention, as they are more likely to become high-risk alcohol drinkers.[16]

This study examined a model incorporating several factors related to the intention to consume alcohol among Dayak adolescents in Sarawak, Malaysia.

Methods

This cross-sectional study has the purpose of exploring the alcohol consumption among Dayak adolescents in Sarawak. The emphasis on the Dayak communities stems from their distinct cultural traits. While numerous native groups reside in Sarawak, each with its own language, traditions, and cultural practices, Dayak people share certain recognizable characteristics. Sample population size was estimated using the precision-based approach single proportion formula, accounting for a 19% base population proportion of current drinkers in Sarawak[17] and a 5% absolute precision. Respondents for this study were randomly selected from male and female respondent houses, with only male or female adolescents approached. The sample size was inflated to reach 1,510 Dayak adolescents, and multistage stratified cluster sampling was used to choose 12 districts from each of the 12 divisions. Face-to-face interviews using an interviewer-administered questionnaire were conducted in Malay, and the questionnaire was pilot-tested to ensure its quality before data collection. Ethics approval from the ethics committee of the Faculty of Medicine and Health Sciences was obtained before data collection. (Ref: UNIMAS/NC-21.02/03-02 JId.4 (55), 20 April 2020).

The study was conducted over 30 months, from September 2019 to February 2022, with a breakdown of different activities that included proposal approval, pretesting and validation, data collection , and analysis. The questionnaire consisted of the following five components: characteristics of respondents (age, education, occupation, marital status, education status, ethnicity, and religion), parental characteristics (age, gender, spouse and child relationships, monthly household income, and family characteristics), Theory of Planned Behavior, alcohol consumption characteristics (including drinking frequency and alcohol misuse), as well as the type of alcoholic beverages consumed (assessed using the AUDIT questionnaire). The Theory of Planned Behavior measures attitude, social norms, perceived behavior control, and intention to consume alcohol. Ten questions were asked to identify the alcohol

use disorder among the Dayak adolescents, commonly known as AUDIT: The Alcohol Use Disorders Identification Test. [18] The AUDIT method was developed as a simple method of screening for excessive drinking and to assist in brief assessment. It has three domains that assess hazardous alcohol use, dependence symptoms, and harmful alcohol use. In the Theory of Planned Behavior (TPB) section, 68 statements were used to predict risky drinking. It measured attitudes, subjective norms, and perceived behavioral control that predict the intention to engage in risky drinking, which in turn predicts future heavy episodic drinking.[19] Back-to-back translation was validated by two language experts, who are expert in both Malay and English languages. All questionnaires were pre-tested in local setting consistency. The Cronbach's alpha reliability coefficient varies from .876 to .946. A measurement model was developed to determine the convergent and discriminant validity of the constructs.[20] Before data collection, informed written consent was obtained from guardians and adolescents. The Structural equation modeling (SEM) was used to establish the causal relationship between attitude, subjective norms, perceived behavior control, intention to use, and alcohol intake among Dayak adolescents. The SEM analysis was used a measurement model (convergent and discriminant validity) and structural model analysis (path analysis). The variance accounted for (VAF) was used to analyze different parameters' indirect and total effects on the variables.[21] Partial least squares were used to analyze the relationship between constructs, with p-values of regression coefficients (F-test) and variance explained (R-squared) as the indicators of the model's explanatory power.[22] Bootstrapping was used to assess the statistical significance of each path.[21]

Results

The socio-demographic characteristics of the participants are listed in Table 1. The survey of 1,510 respondents revealed that the average age of the respondents was 17.3 years, with a slight majority of females (56.6%). The Iban community was the most represented ethnic group (68%), followed by the Bidayuh (14.6%) and the Orang Ulu (5.9%). Christianity was the most widely held religion (91.7%), followed by Islam (5.8%), and Buddhism (2.1%). Most respondents were single (91%), with students constitute the majority of workforce (77.7%). Secondary schooling was the most common level of education (64.5%), followed by pre-university (25.6%; Table 1).

Table 1 Respondents Characteristics (n=1510)

Characteristics	N	%/Mean
Age in years, min, max	1510	17.30 (1.44), 11, 19
Gender		
Male	656	43.4
Female	854	56.6
Ethnicity		
Iban	1026	67.9
Bidayuh	220	14.6
Orang Ulu	89	5.9
§Others	175	11.6
Religion		
Christianity	1385	91.7
Islam	87	5.8
Buddhist	31	2.1
¥Others	7	0.5
Marital status		
Single	1374	91.0
Married	91	6.0
€Others	45	3.0
Occupation		
Student	1174	77.7
Unemployed	42	2.8
Housewife	5	0.3
ξOthers	289	19.1
Education level		
No formal education	10	0.7
Kindergarten	3	0.2
Primary school	47	3.1
Secondary school	974	64.5
Pre-university	386	25.6
Vocational school	6	0.4
ΨOthers	84	5.6

§others include Kayan, Punan, Ngaju, etc; ¥others include Bahai, Animism, etc; €others include separated, divorced etc; ξothers includes employed, self-employed, etc; Ψothers include Diploma, Certificate, etc

Table 2 Alcohol use disorder (n=1510)

Alcohol use disorder	n	%
No risk (0)	174	11
Low-risk (1–7)	752	50
Hazardous (8–15)	465	31
Harmful (16-19)	70	5
Dependence (≥20)	49	3

ξ others include whiskey, sake, tequila, etc.

Results of this study showed that 50.0% of Dayak adolescents consumed alcohol at a low risk, while 31.0% of them consumed alcohol at a hazardous risk. Abstainers comprised only 11.0% of the participants, while a small number (5.0%) exhibited harmful alcohol use, and 3.0% fell under the dependence category (Table 2).

A non-linear algorithm and bootstrapping resampling method were applied to perform a robust path analysis. In this study, give constructs were evaluated to test validity, including physical activity, dietary behavior, perceived behavior control, subjective norm, attitude, intention, and alcohol consumption. The average variance extracted was used to assess convergent validity, with a value greater than 0.50 indicating that the latent construct accounted for most of the variation in the indicators. The AVE extracted ranged from .58 to 1.00, indicating good reliability. Discriminant validity was assessed using three measures: Fornell-Larcker criteria, item cross-loading, and Heterotrait-Monotrait (HTMT) criterion ratio. The standardized root mean squared residual (SRMR) was .09, which was acceptable, and the normed fit index (NFI) was .58, indicating a well-fitted model.

Fig. 1 presents the results of the analysis and the hypothesis decision. Attitude, subjective norm, and perceived behavior control were associated with intention. Attitude (β= .22, p<.001) and subjective norm (β=.33, p<.001) were positively associated with intention, while perceived behavior control (β=−.41, p< .001) was negatively associated with intention. Furthermore, in the population of this study, intention, attitude, and perceived behavior control were also associated with alcohol consumption among Dayak adolescents, with intention (β=.15, p<.001) and attitude (β =.20, p<.001) had a direct positive effect on alcohol consumption and perceived behavior control (β=−.32, p<.001) had a strong negative effect on alcohol consumption. However, no significant association was indentified between the subjective norm and alcohol consumption. Therefore, subjective norms had no association with alcohol consumption among Dayak adolescents in this study (Fig. 1).

Discussion

Analysis in this present study revealed that older Dayak adolescents are more likely

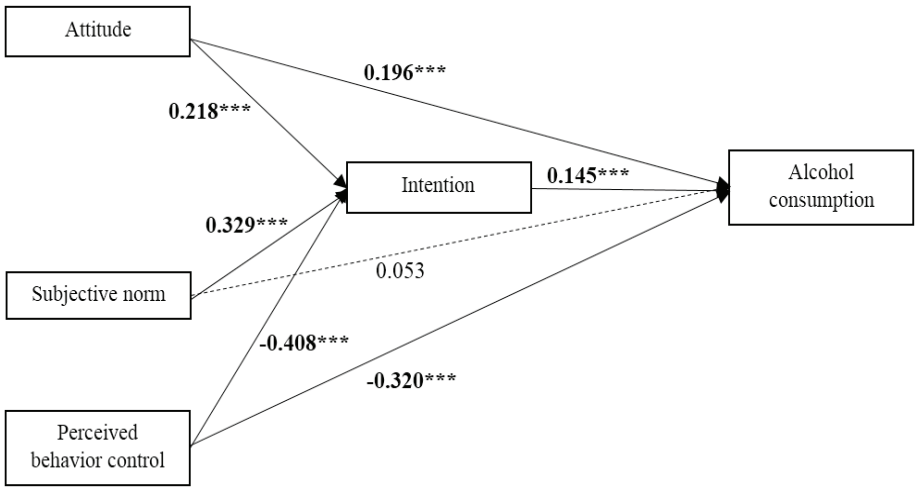

Fig. 1 Structural Path Analysis of Alcohol Consumption, Intention, Attitude, Subjective Norm, and Perceived Behavior Control

to be engaged in alcohol consumption and problematic drinking, which is consistent with a study in Australia.[12] This might be due to the greater availability of alcohol in Sarawak, particularly during social events and festivals, when compared to other areas in Malaysia. However, the study also suggests that the role of direct or indirect availability, such as through parents or family members, should be further investigated.[23] The findings of this study indicate that stronger intentions to drink and higher alcohol consumption are associated with a higher attitude score among Dayak adolescents, contradicting the findings of another study by Sudhinaraset *et al*.[24] The latter found that lower involvement in social networks that use alcohol, less peer persuasion to use, and stronger negotiation skills to resist alcohol use is linked to parental or societal disapproval or negative attitudes towards alcohol use. In this present study, subjective norms are associated with drinking, which aligns with the findings of Pedersen,[25] who found that specific drinking outcomes are linked with perceived descriptive norms or peer's perception of alcohol use. However, further research is needed to assess the perceived injunctive norms, or individuals' perceptions of peers' attitudes towards the acceptability of certain behaviors associated with all drinking outcomes, including the consequences. Perceived behavior control has a negative association with intention and alcohol consumption. While exposure to information about the harmful effects of alcohol is crucial for preventing alcohol consumption, other control factors, such as the legal and economic ways of obtaining alcohol among adolescents, are significantly more beneficial.[11] This TPB model suggests that intention is the strongest predictor of alcohol use. This means that the more someone intends to drink alcohol, the more likely they are to actually do so. Intention is influenced by a number of factors, including attitude, subjective norms, and perceived behavioral control.[26] However, it is important to note that the relationship between intention and behavior could be complex and might be influenced by other factors, such as past drinking behavior and the social environment. Overall, in this study highlights the complex interplay between intention, social environment, and contextual factors in predicting alcohol drinking among Dayak adolescents.

Several limitations should be considered when interpreting the findings of this study. Firstly, cautions should be exercised when generalizing the results to other ethnic groups or regions since the study focuses exclusively on the Dayak adolescents of Sarawak. In addition, relying on self-reported data means that it is susceptible to biases in perception, which may in turn influence the accuracy of the findings.

The cross-sectional design of this study also limits its ability to establish a causal relationship between the independent and dependent variables. Thus, the conclusions drawn from this study should be interpreted with caution, and future research should address these limitations to provide more robust and reliable evidence.

In conclusion, this study has shed light on the alcohol consumption patterns and associated factors among Dayak adolescents in Sarawak. The findings suggest that a significant proportion of Dayak adolescents are engaging in alcohol consumption at either low or hazardous levels, with a small percentage exhibiting harmful or dependent alcohol use. Attitude, subjective norm, and perceived behavior control are associated with intention, while intention, attitude, and perceived behavior control are associated with alcohol consumption among Dayak adolescents. Yet, subjective norms do significantly associate with alcohol consumption. These findings highlight the importance of developing interventions, such as school-based health promotion and targeted screening among adolescent population that focus on changing attitudes, strengthening perceived behavior control, and improving parental and societal disapproval of alcohol consumption. Future research should consider addressing the limitations of this study and exploring the underlying factors that contribute to alcohol consumption among Dayak adolescents in Sarawak.

Acknowledgements

The authors extend their gratitude to UNIMAS for their valuable assistance in conducting this study, especially to the UNIMAS Medical Ethics Committee (Ref: UNIMAS/NC-21.02/03-02 Jld.4 (55)). They would also like to thank the local division offices and councils for granting permission to conduct research in their respective areas. The study was made possible through funding from the Yayasan Dayak Chair Grant (F05/DRC/2051/2020), for which the authors are grateful.

References

1. Zhou Y, Zheng J, Li S, Zhou T, Zhang P, Li HB. Alcoholic beverage consumption and chronic diseases. Int J Environ Res Public Health. 2016;13(6):522. https://doi.org/10.3390/ijerph13060522
2. Squeglia LM, Jacobus J, Tapert SF. The effect of alcohol use on human adolescent brain structures and systems. Handb Clin Neurol. 2014;125:501–10.https://doi.org/10.1016/b978-0-444-62619-6.00028-8
3. Soundararajan S, Narayanan G, Agrawal A, Prabhakaran D, Murthy P. Relation between age at first alcohol drink & adult life drinking patterns in alcohol-dependent patients. Indian J Med Res. 2017;146(5):606–11. https://doi.org/10.4103/ijmr. IJMR_1363_15
4. Center for Disease Control and Prevention. Alcohol and Public Health. 2019. Available from: https://www.cdc.gov/alcohol/index.htm.
5. Wackernah RC, Minnick MJ, Clapp P. Alcohol use disorder: pathophysiology, effects, and pharmacologic options for treatment. Subst Abuse Rehabil. 2014;5:1–12. https://doi.org/10.2147/SAR.S37907
6. Ahmad NA, Mohamad Kasim N, Mahmud NA, Mohd Yusof Y, Othman S, et al. Prevalence and determinants of disability among adults in Malaysia: results from the National Health and Morbidity Survey (NHMS) 2015. BMC Public Health. 2017;17(1):756. https://doi.org/10.1186/s12889-017-4793-7
7. NoorAni A, Rajini S, Balkish MN, Noraida MK, SMaria A, Fadhli MY, et al. Morbidity patterns and healthcare utilisation among older people in Malaysia: 1996-2015. Public Health. 2018;163:105–12. https://doi.org/10.1016/j.puhe.2018.06.018
8. Institute of Public Health. National Health and Morbidity Survey 2015 (NHMS 2015). Vol. II: Non-Communicable Diseases, Risk Factors & Other Health Problems; 2015. Kuala Lumpur: Institute of Public Health; 2015. Available from: http://iku.moh.gov.my/index.php/research-eng/list-of-research-eng/iku-eng/nhms-eng/nhms-2015. Accessed MOH/S/IKU/52.15(RR).
9. Cooke R, Dahdah M, Norman P, French DP. How well does the theory of planned behaviour predict alcohol consumption? A systematic review and meta-analysis. Health Psychol Rev. 2016;10(2):148–67.https://doi.org/10.1080/17437199.2014.947547
10. Cutrín O, Mac Fadden I, Ayers SL, Kulis SS, Gómez-Fraguela JA, Marsiglia FF. Applicability of the theory of planned behavior for predicting alcohol use in Spanish early adolescents. Int J Environ Res Public Health. 2020;17(22):8539. https://doi.org/10.3390/ijerph17228539
11. Davies EL, Paltoglou AE, Foxcroft DR. Implicit alcohol attitudes predict drinking behaviour over and above intentions and willingness in young adults but willingness is more important in adolescents: Implications for the Prototype Willingness Model. Br J Health Psychol. 2017;22(2):238–53. doi:10.1111/bjhp.12225
12. Zhao X, Kelly AB, Rowland B, Williams J, Kremer P, Mohebbi M, Carter R, et al. Intention to drink and alcohol use before 18 years among Australian adolescents: An extended Theory of Planned Behavior. Addict Behav. 2020;111:106545. https://doi.org/10.1016/j.addbeh.2020.106545
13. Chung LM, Fong SS. Predicting actual weight loss: A review of the determinants according to the theory of planned behaviour. Health Psychology Open. 2015;2(1):2055102914567972. https://doi.org/10.1177/2055102914567972
14. Jiang H, Xiang X, Hao W, Room R, Zhang X, Wang X. Measuring and preventing alcohol use and related harm among young people in Asian countries: a thematic review. Glob Health Res Policy. 2018;3:14. https://doi.org/10.1186/s41256-018-0070-2
15. Carvajal F, Lerma-Cabrera JM. Alcohol consumption among adolescents - implications for public health. In: Claborn D, ed. Topics in Public Health; 2015. p. 51–76.
16. Hong JW, Noh JH, Kim DJ. The prevalence of and factors associated with high-risk alcohol consumption in Korean adults: The 2009-2011 Korea National Health and Nutrition Examination Survey. PLoS One. 2017;12(4):e0175299. https://doi.org/10.1371/journal.pone.0175299
17. Institute of Public Health. National Health and Morbidity Survey (NHMS) 2017: Key Findings from the Adolescent Health and Nutrition Surveys. Kuala Lumpur: Institute of Public Health,; 2018. Available from: http://iku.moh.gov.my/index.php/research-eng/list-of-research-eng/iku-eng/nhms-eng/nhms-2017. Accessed MOH/S/IKU/108.18(BOT).

18. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care. Geneva: World Health Organization; 2001. Available from: https://www.who.int/publications/i/item/WHO-MSD-MSB-01.6a
19. Collins SE, Witkiewitz K, Larimer ME. The theory of planned behavior as a predictor of growth in risky college drinking. J Stud Alcohol Drugs. 2011;72(2):322–32. doi:10.15288/jsad.2011.72.322
20. Sarstedt M, Ringle C, Hair J. Partial least squares structural equation modeling. Handbook of market research. New York: Springer; 2017.
21. Hair J, Hult GTM, Ringle C, Sarstedt M. A primer on partial least squares structural equation modeling (PLS-SEM). New York: SAGE Publications; 2016.
22. Dijkstra TK, Henseler J. Consistent partial least squares path modeling. MIS Quarterly. 2015;39(2):297–316. https://doi.org/10.25300/MISQ/2015/39.2.02
23. Rodzlan Hasani WS, Saminathan TA, Ab Majid NL, Miaw Yn JL, Mat Rifin H, Abd Hamid HA, et al. Polysubstance use among adolescents in Malaysia: Findings from the National Health and Morbidity Survey 2017. PLoS One. 2021;16(1):e0245593. https://doi.org/10.1371/journal.pone.0245593
24. Sudhinaraset M, Wigglesworth C, Takeuchi DT. Social and cultural contexts of alcohol use: influences in a social-ecological framework. alcohol research. Current Rev. 2016;38(1):35–45.
25. Pedersen ER, Osilla KC, Miles JN, Tucker JS, Ewing BA, Shih RA, et al. The role of perceived injunctive alcohol norms in adolescent drinking behavior. Addict Behav. 2017;67:1–7. doi:10.1016/j.addbeh.2016.11.022
26. Hamilton HR, Armeli S, Tennen H. To drink or not to drink: When drinking intentions predict alcohol consumption and consequences. Br J Health Psychol. May 2022;27(2):516–33. https://doi.org/10.1111/bjhp.12560

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Original Article

Comparative Evaluation of Effectiveness of Rocuronium Bromide vs. Succinyl Choline on Quality of Intubating Conditions during General Anesthesia

Aditi Burkul,[1] Nazima Memon,[2] Vaishnavi Kulkarni[3]

[1]Department of Anesthesiology, Tata Memorial Hospital, Mumbai, India
[2]Department of Anesthesiology, Government Medical College, Aurangabad, India
[3]Department of Anesthesiology, Dr. Shankarrao Chavan Government Medical College, Nanded, India

Article History

Received: July 13, 2023
Accepted: October 23, 2023
Published: October 30, 2023

DOI: 10.15850/ijihs.v11n2.3457
IJIHS. 2023;11(2):70–78

Correspondence:
Aditi Burkul,
Department of Anesthesiology
Tata memorial hospital, Mumbai, India
Email: aditii.burkul@gmail.com

Abstract

Objectives: To compare the quality of intubating conditions and hemodynamic responses to the administration of Rocuronium Bromide and Succinyl Choline during general anesthesia.

Methods: This was a comparative study conducted at the anesthesiology department of a tertiary care medical college. Sixty patients undergoing various surgeries under general anesthesia were included in this study based on predefined inclusion and exclusion criteria. Patients were divided into Group S (receiving succinylcholine) and Group R (receiving rocuronium). In all patients, the quality of intubating conditions was assessed. Excellent or good conditions were considered to be acceptable intubating conditions, whereas fair and poor conditions were considered unacceptable.

Results: Mean age, weight, gender distribution, and ASA grades were comparable in both groups. The overall quality of intubation was found to be better in group S than in group R, and the difference was statistically significant ($p=0.004$). The duration of action was significantly longer in group R than in group S ($p<0.001$). Hemodynamic stability was comparable in both the groups, except for heart rate at 10 min, which was higher in Group R than in Group S. Incidence of fasciculation was significantly more in Group S as compared to Group R, and the difference was found to be highly significant ($p=0.0001$).

Conclusion: Succinylcholine for rapid sequence intubation is associated with better intubation conditions than rocuronium.

Keywords: Intubation, muscle relaxant, rocuronium, succinylcholine

Introduction

Rapid and safe endotracheal intubation is of paramount importance in practice of general anesthesia. Adequate intubating conditions are required to avoid airway trauma and adverse sympathetic responses. With the advent of muscle relaxations, the anesthesia practice changed drastically for better. First muscle relaxant for surgery, d-tubocurarine, was introduced in 1942.[1] With this relaxant, jaw relaxation could easily be obtained to facilitate the orotracheal intubation. Soon afterwards, this invention had inspired R.R. Macintosh to invent the famous Macintosh laryngoscope in 1943.[2] Although d-tubocurarine could produce jaw relaxation to facilitate orotracheal and nasotracheal intubation, it brought with it, its own drawback. It produced muscarinic block and ganglion block leading to tachycardia and hypotension.[3] The onset of action was also delayed, taking up to 3 minutes to produce good intubating condition. This created a problem in emergency cases and full stomach cases, where rapid procurement of airway is priority to avoid regurgitation

and aspiration. Soon after, in 1954, studies have reported manifold increase in mortality in patients receiving dTC than those who had not received muscle relaxation, thereby underlining the risks involved in using muscle relaxants for intubation.[4] Succinyl choline has been a famous muscle relaxant available for rapid sequence induction of anesthesia where securing the airway quickly, such as in cases with full stomach requiring emergency surgeries, is of critical importance.[5] However, the use of depolarizing muscle agents, such as, succinylcholine was found to be associated with risk of hyperkalemia, variable increase in the intracranial pressure and intraocular pressure. Moreover, succinyl choline is also contraindicated in patients suffering from burns, crush injuries, muscular dystrophies, severe denervation syndrome, malignant hyperthermia, abdominal sepsis, or allergy to succinyl choline in susceptible patients and development of phase II block after a large dose or continuous infusion. The duration of succinylcholine chloride was prolonged in patients with pseudo cholinesterase deficiency. All these conditions, where the use of succinyl choline was contraindicated, has led scientists to look for newer drugs which can be used as an alternative to succinyl choline.[6] In 1967, a first study that reported on clinical administration of the synthetic amino steroid pancuronium was published. The intermediate-acting neuromuscular blocker was built on the compound's metabolism and resulted in the introduction of vecuronium, an amino steroid which is also a mono-quaternary analogue of pancuronium and atracurium that is a benzylisoquinolinium, into clinical practices in the 1980s. However, none of these nondepolarizing muscle relaxants could match succinyl choline with respect to the onset of action.[7] Although various methods, such as the use of the "priming" (divided dose) technique and the use of larger doses of atracurium and vecuronium, had been tried in an attempt to reduce the onset time of these neuromuscular blockers, these methods had either proved to be unsuccessful or hazardous to the patient, as in the case of the priming technique, or resulted in a long duration of action with the use of larger doses. In 1990, a new non-depolarizing muscle relaxant, Rocuronium Bromide, which challenged the onset time of Succinyl choline in facilitating safe and rapid endotracheal intubation, was introduced.[8] Rocuronium bromide is safe as there are no side effects such as histamine release, which is unlike other non-depolarizing muscle relaxants. This drug also maintains cardiovascular stability and is known for rapid recovery. It provides intubating conditions similar to those of succinyl choline 60 to 90s after administration. The dose of rocuronium usually defines onset time, duration, and intubating conditions. This study aimed to evaluate the quality of intubating conditions with rocuronium bromide and to compare it with that of succinylcholine for use in general anesthesia in adult patients.

Methods

This was a comparative study performed at the anesthesiology department of a tertiary care medical college in Maharashtra, India. The duration of study was 2 years, from January 2021 to December 2022. Sixty (60) patients undergoing various surgeries under general anesthesia during that period, such as laparoscopic appendectomy, laparoscopic cholecystectomy, tonsillectomy, laparoscopic ovarian cystectomy, and modified radical mastectomy. Patients who underwent elective surgeries under general anesthesia with ASA Grades I and II and Mallampati score of I and II were included in this study. Patients who refused to participate, those with Mallampati score of I and II as well as patients with ASA grade III and above were excluded from the study. Patients with known allergies to anesthetic drugs and serious comorbids were also excluded from the study. The institutional ethical committee approved the study and written informed consent was obtained from all the participants. The sample size was calculated on the basis of a pilot study done by Panda *et al*. by assuming 90% power and 95% confidence interval. The sample size required was 19 patients per arm (total n=38). Based on the central limit theorem, sample size was determined to be adequate if it was more than 25; thus, 30 patients were included in each group. Computer based randomization was used for randomization and anesthetists were blinded to the allocation information. Group S received intravenous Succinylcholine 1.5mg/kg while Group R received intravenous Rocuronium bromide 0.6mg/kg. All patients were thoroughly evaluated and intravenous cannula was secured with a 20G IV line. Patients were transferred to the operating room and IV fluid was started. Continuous monitoring of patients for heart rate, systolic and diastolic blood pressures, ECG, SPO2, and ETCO2 was also started. Patients were also premedicated with Inj. Glycopyrrolate 4 mcg/kg IV, as well as

with Inj.Midazolam0.05mg/kg IV and Fentanyl 2mcg/kg. Preoxygenation of 3 minutes was followed by induction with Inj. Propofol 2mg/kg IV Both drugs, either rocuronium bromide (Group R) or succinyl choline (Group S), were given to patients depending on the assigned group. Surgery commenced at 60 seconds in every patient. Patients were intubated with a cuffed endotracheal tube no. 7.0/8.0. In all patients, the quality of intubating conditions was assessed by using Cooper *et al.*[9] scoring system. The intubating conditions were divided into excellent (jaw relaxed, vocal cords apart and immobile, no diaphragmatic movements), good (jaw relaxed, vocal cords apart and immobile, some diaphragmatic movements), fair (jaw relaxed, vocal cords moving, "bucking"), or poor (jaw not relaxed; vocal cords closed). Excellent or good conditions were considered acceptable intubating conditions, while poor and inadequate conditions were regarded as unacceptable intubating conditions. During surgery, the anesthesia was maintained with oxygen, nitrous oxide (33:67), isoflurane, and intermittent positive pressure ventilation. The hemodynamic stability was then assessed by continuous monitoring of HR, saturation, and mean arterial pressure preoperatively and immediately after intubation, followed by monitoring at 10 min, 20 min, 30 min and 40 min after intubation. The side effects such as tachycardia, bradycardia, histamine release and laryngospasm, arrhythmia, and muscle fasciculation were noted in all cases. Duration of action of muscle relaxants was considered to be extending until recovery of spontaneous respiration. At the end of the procedure, all patients were reversed using neostigmine 0.04 mg/kg and Glycopyrrolate 0.005 mg/kg titrated to response and patient was extubated. SPSS 23.0 was used for data analysis. Descriptive statistics were elaborated in the form of means and standard deviations for continuous variables, while frequencies and percentages were used for categorical variables. Group comparisons were made using independent sample t-test for continuously distributed data and chi-square test for categorical data. Repeated observations were compared using paired t-test or repeated measures ANOVA as applicable. A P-value of less than 0.05 was taken as statistically significant.

Results

The two groups were compared for mean age, weight, gender distribution, and ASA Grades. The mean age of cases in group R and group S was found to be 35.12 +/- 7.46 and 32.34 +/- 6.98 years, respectively. The mean weight of patients in group R and S was found to be 62.34 +/- 7.86 kg and 60.12 +/- 6.98 kg, respectively. The mean age, weight, gender distribution, and ASA grades were found to be comparable in both groups with no statistically significant difference in any of these parameters. The Mallampati classification score of both the groups were also found to be comparable in both groups with no statistically significant difference ($p>0.05$; Table 1).

The most common surgery performed among participants in group R was laparoscopic appendectomy (33.33%) whereas in group S, laparoscopic cholecystectomy (36.67%) was more common. Overall, the most common surgery was laparoscopic cholecystectomy (33.33%), which was followed by laparoscopic cholecystectomy (31.67%). Other surgeries undertaken were Laparoscopic ovarian cystectomy (13.33%), tonsillectomy (11.67%), and Modified radical mastectomy (10%) (Fig. 1).

The comparison of the quality of intubating

Table 1 Comparison of Mean Age, Weight, Gender, ASA and MPC Grades in Patients

		Group R	Group S	p-value
Mean Age		35.12 +/- 7.46	32.34 +/- 6.98	0.079
Gender Distribution	Males	22 (73.33%)	17 (56.7%)	0.279
	Females	8 (26.66%)	13 (43.3%)	
Weight		62.34 +/- 7.86	60.12 +/- 6.98	0.079
ASA Grade	Grade I	22 (73.33%)	24 (80 %)	0.902
	Grade II	8 (26.66%)	6 (20%)	
MPC Grade	MPC I	16 (53.33%)	21 (70%)	0.288
	MPC II	14 (46.66%)	9 (30%)	

Table 2 Comparison of Quality of Intubating Conditions in Studied Cases

		Group			Fisher's Exact Test	
		R (n=30)	S (n=30)	Total (n=60)	$\chi 2$	P Value
Jaw Relaxation	Score 0	0	0	0	-	-
	Score 1	0	0	0	-	-
	Score 2	5 (16.7%)	0 (0.0%)	5 (8.3%)	5.455	0.052
	Score 3	25 (83.3%)	30 (100.0%)	55 (91.7%)		
Vocal Cord Position	Score 0	0	0	0	13.098	<0.001
	Score 1	4 (13.3%)	0 (0.0%)	4 (6.7%)		
	Score 2	13 (43.3%)	4 (13.3%)	17 (28.3%)		
	Score 3	13 (43.3%)	26 (86.7%)	39 (65.0%)		
Intubation Response	Score 0	0	0	0	8.182	0.012
	Score 1	6 (20.0%)	0 (0.0%)	6 (10.0%)		
	Score 2	12 (40.0%)	10 (33.3%)	22 (36.7%)		
	Score 3	12 (40.0%)	20 (66.7%)	32 (53.3%)		

conditions between the two groups showed that better jaw relaxation was seen in Group S, when compared to Group R; however, this difference was not found to be statistically significant. However, the analysis of two other parameters, vocal cord position and intubation response, showed that both parameters were better in Group S when compared to Group R, and the difference was statistically significant ($p<0.05$; Table 2).

Comparison of both groups on the basis of total score for quality of intubation showed that the mean total scores in Group R and Group S was 7.33 +/- 1.37 and 8.50 +/- 0.68, respectively. Group S had a better total score as compared to Group R, and the difference between the two groups in terms of Total Score was found to be significant (W=222.000, p=<0.001) The analysis of patients in both groups on the basis of duration of action (in minutes) of muscle relaxants showed that the mean durations of action in group R and group S were 22.93 +/- 5.45 and 11.97 +/- 1.71, respectively. The duration of action was longer in group R when compared to group S, and the difference was significant ($p<0.001$; Table 3).

The comparison of both the groups on the basis of quality of intubation showed that most of the patients in Group S had excellent

Table 3 Comparison of Mean Score of Quality of Intubation and Duration of Action in Both Groups

Mean Score of Quality of Intubation and Duration of Action		Group		Wilcoxon-Mann- Whitney U Test	
		R	S	W	p-value
Mean Score of Quality of Intubation	Mean (SD)	7.33 +/- 1.37	8.50 +/- 0.68	222.000	<0.001
	Median (IQR)	8 (6-8)	9 (8-9)		
	Range	5–9	7–9		
Duration of Action (Minutes)	Mean (SD)	22.93 +/- 5.45	11.97 +/- 1.71	899.000	<0.001
	Median (IQR)	22 (18.25–25)	12 (11–13)		
	Range	15–38	7–15		

Table 4 Comparison of Groups on the Basis of Overall Quality of Intubation and Acceptable Grades

Overall Quality of Intubation and Acceptable Grade		Group			Fisher's Exact Test	
		R (n=30)	S (n=30)	Total (n=60)	χ2	p-value
Overall Quality of Intubation	Excellent	16 (53.3%)	27 (90.0%)	43 (71.7%)	10.583	0.004
	Good	10 (33.3%)	3 (10.0%)	13 (21.7%)		
	Fair	4 (13.3%)	0 (0.0%)	4 (6.7%)		
Acceptable Grade	Yes	26 (86.7%)	30 (100.0%)	56 (93.3%)	4.286	0.112
	No	4 (13.3%)	0 (0.0%)	4 (6.7%)		

quality of intubation (90%) whereas good and fair quality was seen in 13 (21.7%) and 4 (6.7%) patients, respectively. In group R, excellent quality of intubation was seen in 16 (53.3%) patients. Overall quality of intubation was found to be better in group S as compared to group R, and the difference was statistically significant (P=0.004). Fisher's exact test was used to explore the association between the 'Group' and 'Acceptable Grade'. In group R, 26 (86.7%) patients had acceptable grades, whereas in group S, all 30 (100%) patients were found to have acceptable grades. Though comparatively less patients had acceptable grades in group R as compared to group S, the difference between groups in terms of distribution of acceptable grade was not found to be significant (χ2=4.286, p=0.112) (Table 4). Both groups were compared for heart rate, SPO2, and also mean arterial pressure pre-operatively and postoperatively, and until 12 hours. The heart rate was found to be comparable at all times, except for the rate at 15 minutes (P<0.05). Mean arterial pressure and SPO2 were found to be comparable in both groups at all the times with no statistically significant difference at any point in time (p>0.05; Table 5).

The analysis of side effects in both groups and their comparison showed that in group R 28 (93.33%) patients did not have any adverse effects while two (6.66%) patients developed tachycardia. In group S, one (3.33%) patient developed bradycardia. Muscle fasciculation's were seen in 24 (80%) of the patients in group S, whereas no patient in Group R developed fasciculation. Incidence of fasciculation was significantly more in group S when compared to Group R, and the difference was found to be highly significant (P=0.0001). Other side effects were comparable in both the groups.

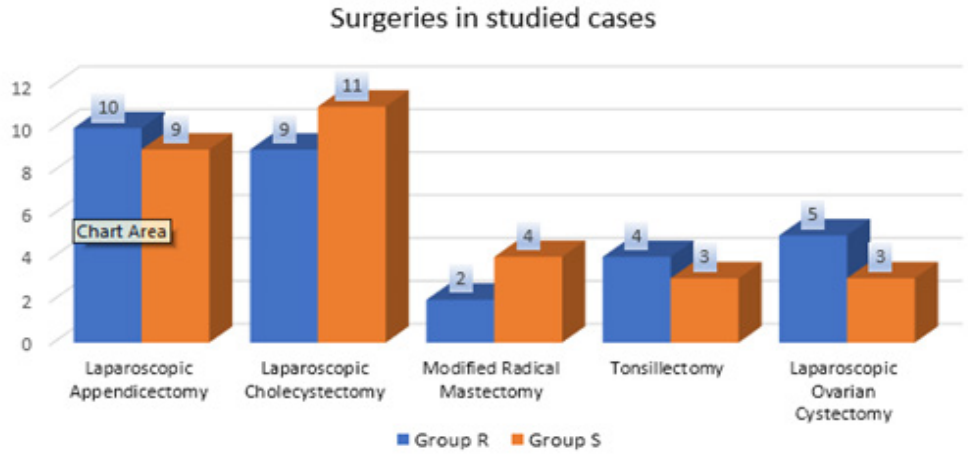

Fig. 1 Types of Surgeries in Studied Cases

Table 5 Comparison of Mean Heart Rate, Mean Arterial Pressure, and SPO_2

Heart Rate(BPM)		Group		P value (Wilcoxon-Mann- Whitney Test)
		Group R Mean (SD)	Group S Mean (SD)	
Heart Rate (BPM)	0 Min	84.12 +/- 8.98	82.36 +/- 8.12	p>0.05
	15 Min	86.28 +/- 9.12	76.42 +/- 8.34	p=0.0001
	30 Min	84.30 +/- 9.80	86.34 +/- 9.12	p>0.05
	1 Hr	82.07 +/- 9.04	84. 36 +/- 9.90	p>0.05
	2 Hr	83.74 +/- 8.18	82.46 +/- 8.86	p>0.05
	3 Hr	81.83 +/- 10.12	84.62+/- 8.12	p>0.05
	4 Hr	80.12 +/- 9.90	82.42 +/- 7.98	p>0.05
	5 Hr	82.86 +/- 10.12	84.34 +/- 8.84	p>0.05
	6 Hr	80.46 +/- 9.70	80.12 +/- 9.12	p>0.05
	7 Hr	78.34 +/- 9.34	80.34 +/- 8.12	p>0.05
	8 Hr	82.30 +/- 10.30	78.64 +/- 6.34	p>0.05
	9 Hr	84.12 +/- 6.82	82.34 +/- 6.58	p>0.05
	10 Hr	80.34 +/- 5.54	82.66 +/- 7.14	p>0.05
	11 Hr	78.54 +/- 6.12	80.12 +/- 6.78	p>0.05
	12 Hr	76.86 +/- 5.90	78.34 +/- 7.10	p>0.05
Mean Arterial Pressure	0 Min	90.92 +/- 8.34	89.03 +/- 8.10	p>0.05
	15 Min	92.34 +/- 8.24	96.87 +/- 10.24	p>0.05
	30 Min	96.96 +/- 9.12	93.37 +/- 9.48	p>0.05
	1 Hr	94.34 +/- 8.48	92.50 +/- 8.68	p>0.05
	2 Hr	96.24 +/- 9.34	91.70 +/- 7.78	p>0.05
	3 Hr	95.34 +/- 8.34	90.73 +/- 7.24	p>0.05
	4 Hr	92.20 +/- 9.84	94.40 +/- 8.12	p>0.05
	5 Hr	90.94 +/- 8.86	88.68 +/- 8.34	p>0.05
	6 Hr	88.34 +/- 9.12	86.34 +/- 9.12	p>0.05
	7 Hr	86.68 +/- 9.34	84.68 +/- 9.02	p>0.05
	8 Hr	88.54 +/- 9.12	90.34 +/- 10.34	p>0.05
	9 Hr	92.34 +/- 9.46	92.46 +/- 8.98	p>0.05
	10 Hr	90.86 +/- 8.24	90.34 +/- 9.46	p>0.05
	11 Hr	91.34 +/- 9.12	90.48 +/- 10.02	p>0.05
	12 Hr	90.56 +/- 9.02	88.62 +/- 9.90	p >0.05
Spo2	0 Min	99.6 +/- 0.48	99.4 +/- 0.86	p>0.05
	15 Min	99.4 +/- 0.86	99.54 +/- 0.74	p>0.05
	30 Min	99.6 +/- 0.48	99.60 +/- 0.48	p>0.05
	1 Hr	99.6+/- 0.48	99.20 +/- 0.72	p>0.05
	2 Hr	99.4 +/- 0.86	99.60 +/- 0.48	p>0.05
	3 Hr	99.2 +/- 0.74	99.40 +/- 0.86	p>0.05
	4 Hr	99.6 +/- 0.48	99.60 +/- 0.48	p>0.05

Table 5 (Continued)

	Heart Rate(BPM)	Group R Mean (SD)	Group S Mean (SD)	P value (Wilcoxon-Mann- Whitney Test)
Spo2	5 Hr	99.0 +/- 0.98	99.4 +/- 0.86	p>0.05
	6 Hr	98.80 +/- 1.12	99.2 +/- 0.74	p>0.05
	7 Hr	99.40 +/- 0.86	99.40 +/- 0.86	p>0.05
	8 Hr	99.60 +/- 0.48	98.12 +/- 0.74	p>0.05
	9 Hr	99.40 +/- 0.86	99.40 +/- 0.86	p>0.05
	10 Hr	99.60 +/- 0.48	99.60 +/- 0.48	p>0.05
	11 Hr	99.40 +/- 0.86	99.46 +/- 0. 46	p>0.05
	12 Hr	99.60 +/- 0.48	99. 34 +/- 0.84	p>0.05

Discussion

Rapid and safe endotracheal intubation is of paramount importance in practice of general anesthesia. The only muscle relaxant famous for its rapid onset of action was succinyl choline until the discovery of rocuronium bromide. The quest to find alternatives to succinyl choline has led scientist to look for new drug, and that is when rocuronium bromide, non-depolarizing muscle relaxant became famous for its comparable time of onset of action.[10] The newer drug also help overcome the side effects associated with succinyl choline, such as bradycardia, arrhythmias, hyperkalemia, variable increase in intraocular, intragastric and intracranial pressures. In the effort to compare the effectiveness of Rocuronium Bromide and Succinyl Choline, intubating conditions were assessed in this study. In this study, the comparison of quality of intubating conditions showed that vocal cord position and intubation response showed that both of these parameters are better in Group S than in Group R, and the difference is statistically significant (p<0.05). Tran DT *et al.* conducted an extensive literature review to determine whether rocuronium creates intubating conditions comparable to those of succinylcholine during RSI intubation.[11] For this purpose, they reviewed 37 randomized controlled trials (RCTs) or controlled clinical trials (CCTs) related to the use of rocuronium and succinylcholine. The study discovered that, overall, succinylcholine is superior to rocuronium for achieving excellent intubating conditions(RR 0.86 [95% CI, 0.81 to 0.92; n=4151] and clinically acceptable intubation conditions (RR 0.97, 95% CI, 0.95 to 0.99; n = 3992, 48 trials]). On the basis of these findings they concluded thatsuccinylcholine created superior intubation conditions to rocuronium in achieving excellent and clinically acceptable intubating conditions. Similar findings are also reported by other authors such as Guihard B *et al*[12] and Chavan SG *et al*.[13]

The analysis of patients in both groups on the basis of duration of action of muscle relaxants showed that the mean durations of action in group R and group S was 22.93 +/- 5.45 and 11.97 +/- 1.71 minutes, respectively. The longer duration of action was observed in group R as compared to group S, and the difference was highly significant (p<0.001). Magorian T *et al* undertook a study to compare rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients.[14] In their study, fifty patients, ASA 1-3, were randomly designated to receive one of three intravenous doses of rocuronium (0.6, 0.9, and 1.2 mg/kg), vecuronium (0.1 mg/kg), or succinylcholine (1.0 mg/kg). Also, the time from injection of muscle relaxant until complete ablation of T1 (onset) and recovery of T1 to 25% (duration) were also recorded. The study found that the clinical duration of action was longest with 1.2 mg/kg rocuronium, which was similar with 0.6 and 0.9 mg/kg rocuronium, and vecuronium, and was least with succinylcholine. These findings are similar to this present study's findings. Similar findings were also reported by authors such as Li G *et al.*[15] and Sparr HJ *et al*.[16] The comparison of hemodynamic parameters in both groups demonstrated that the heart rate was found to be comparable at all the times, except at 10 minutes (p<0.05). Mean arterial pressure and SPO2 were found to be

comparable in both groups at all the times with no statistically significant difference at any point in time (p>0.05). Lenin *et al*.[17] undertook a study to compare the onset time, duration of action, intubating condition, and the hemodynamic effects of rocuronium bromide at the dose of 0.8 mg/kg and Succinylcholine at the dose of 1.5 mg/kg. The study found that both drugs raised mean heart rate, systolic blood pressure, diastolic blood pressure, and MAP from intubation to subsequent intervals; however, despite being comparable, this increase is not statistically significant different between the groups. Similar hemodynamic comparability between succinylcholine and rocuronium is also reported by other authors such as Sorensen *et al*.[18] and Li *et al*.[19] The analysis of cases on the basis of adverse effects showed that the incidence of fasciculation is significantly more in group S as compared to Group R, and the difference is highly significant (p=0.0001). Other side effects are comparable in both groups. Twenty four (24, 80%) patients in group S experienced muscle fasciculation, while none in group R experienced this. Similar findings are also reported by Zhang *et al*.[20]

Small number of cases and the use of fixed dose of rocuronium are the limitations of our study. A similar study with larger cohort will further substantiate the findings of this study. In conclusion, the use of succinylcholine for rapid sequence intubation is found to be associated with better intubation conditions as compared to rocuronium.

References

1. Spirova EN, Ivanov IA, Kasheverov IE, et al. Curare alkaloids from Matis Dart Poison: Comparison with d-tubocurarine in interactions with nicotinic, 5-HT3 serotonin and GABAA receptors. PLoS One. 2019; 14(1):e0210182. doi:10.1371/journal.pone.0210182.
2. Bhat R, Sanickop CS, Patil MC, Umrani VS, Dhorigol MG. Comparison of Macintosh laryngoscope and C-MAC video laryngoscope for intubation in lateral position. J Anaesthesiol Clin Pharmacol. 2015;31(2):226–9. doi:10.4103/0970-9185.155221.
3. Patel S, Shukla J, Jain S, Paliwal V, Tripathi N, Paliwal S, et al. Repositioning of tubocurarine as analgesic and anti-inflammatory agent: Exploring beyond myorelaxant activity. Biochem Pharmacol. 2022;205:115248. doi:10.1016/j.bcp.2022. 115248
4. Martini CH, Honing GHM, Bash LD, Olofsen E, Niesters M, van Velzen M, et al. The use of muscle relaxants and reversal agents in a setting without cost restrictions: experience from a Tertiary Academic Hospital in the Netherlands. Ther Clin Risk Manag. 2022;18:379-90. doi:10.2147/TCRM.S350314.
5. Bohringer C, Moua H, Liu H. Is there still a role for succinylcholine in contemporary clinical practice?. Transl Perioper Pain Med. 2019; 6(4):129-35. doi:10.31480/2330-4871/100
6. Luxen J, Trentzsch H, Urban B. Rocuronium und Sugammadex in der Notfallmedizin: Anforderungen an ein Muskelrelaxans für die “rapid sequence induction” [Rocuronium and sugammadex in emergency medicine: requirements of a muscle relaxant for rapid sequence induction]. Anaesthesist. 2014; 63(4):331–7. doi:10.1007/s00101-014-2303-1
7. Mørk EL, Kristensen ML, Stokholm JB, Söderström CM, Madsen MV, Gätke MR. Resistance towards nondepolarising muscle relaxants: prolonged onset time: A systematic review. Eur J Anaesthesiol. 2019; 36(7):477–85. doi:10.1097/EJA.0000000000000991
8. Tachikawa M, Asai T, Okuda Y. Rocuronium bromide intravenous solution maruishi is more suitable than ESLAX intravenous during rapid-sequence induction of anesthesia. J Anesth. 2019; 33(5):600–3. doi: 10.1007/s00540-019-02673-x.
9. Cooper R, Mirakhur RK, Clarke RS, Boules Z. Comparison of intubating conditions after administration of Org 9246 (rocuronium) and suxamethonium. Br J Anaesth. 1992; 69(3):269–73. doi:10.1093/bja/69.3.269
10. Yuan H, Zhang S, Yin L, Luo T, Zhang R, Wu S. The safety of high-dose rocuronium bromide in general anesthesia for spinal surgery and its effects on muscle relaxation. Am J Transl Res. 2021;13(7):8110–7.
11. Tran DT, Newton EK, Mount VA, Lee JS, Wells GA, Perry JJ. Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev. 2015;2015(10):CD002788. doi:10.1002/14651858.CD002788.pub3
12. Guihard B, Chollet-Xémard C, Lakhnati P,

Vivien B, Broche C, Savary D, et al. Effect of rocuronium vs succinylcholine on endotracheal intubation success rate among patients undergoing out-of-hospital rapid sequence intubation: a randomized clinical trial. JAMA. 2019; 322(23):2303–12. doi:10.1001/jama.2019.18254

13. Chavan SG, Gangadharan S, Gopakumar AK. Comparison of rocuronium at two different doses and succinylcholine for endotracheal intubation in adult patients for elective surgeries. Saudi J Anaesth. 2016; 10(4):379–83. doi:10.4103/1658-354X.177330
14. Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. Anesthesiology. 1993;79(5):913–18. doi:10.1097/00000542-199311000-00007
15. Li G, Cheng L, Wang J. Comparison of rocuronium with succinylcholine for rapid sequence induction intubation in the Emergency Department: a retrospective study at a Single Center in China. Med Sci Monit. 2021;27:e928462. doi:10.12659/MSM.928462
16. Wilson JW, Gillen JP, Maute T. Patient safety during rapid sequence intubation when using succinylcholine instead of nondepolarizing paralytic agents: should we change a common rapid sequence intubation pathway?. J Emerg Trauma Shock. 2020;13(4):264–68. doi:10.4103/JETS.JETS_92_18
17. Lenin P, Rajaraman R, Stalin R, Manikandan G. A comparative study between rocuronium and succinylcholine in evaluating endotracheal intubating conditions in day care surgeries. IAIM, 2022;9(1): 34–9.
18. Marsch SC, Steiner L, Bucher E, Pargger H, Schumann M, Aebi T, et al. Succinylcholine versus rocuronium for rapid sequence intubation in intensive care: a prospective, randomized controlled trial. Crit Care. 2011;15(4):R199. doi:10.1186/cc10367
19. Sørensen MK, Bretlau C, Gätke MR, Sørensen AM, Rasmussen LS. Rapid sequence induction and intubation with rocuronium-sugammadex compared with succinylcholine: a randomized trial. Br J Anaesth. 2012;108(4):682–9. doi:10.1093/bja/aer503
20. Zhang Z, Zhang DS, Sui W, Liu XH, Zhang L, Sun JH. Effects of pretreatment with different doses of cisatracurium on succinylcholine-induced fasciculations. Int J Clin Pharmacol Ther. 2016;54(6):426–32. doi:10.5414/CP202531

Original Article

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Thyroid Profile and Serum Lipid Level in Women with Normal Pregnancy

Raj Kumar,[1] Sudeep Kumar,[1] Manisha Arora,[2] Dinesh Kumar,[1] Sumesh Prasad Sah,[1] Shivani Sharma[3]

[1]Department of Biochemistry, Muzaffarnagar Medical College, Muzaffarnagar, Uttar Pradesh, India
[2]Department of Biomedical Sciences, Mercer University School of Medicine, Columbus, Georgia, USA
[3]Department of Physiology Medical University of the Americas, Nevis

Article History

Received: July 14, 2023
Accepted: October 12, 2023
Published: October 30, 2023

DOI: 10.15850/ijihs.v11n2.3460
IJIHS. 2023;11(2):79–84

Correspondence:
Sudeep Kumar
Department of Biochemistry, Muzaffarnagar Medical College, Muzaffarnagar, Uttar Pradesh, India
Email: sudeepty@gmail.com

Abstract

Objective: To evaluate the changes in thyroid profile and serum lipid level in normal pregnancy.

Methods: This observational study was conducted at the Department of Biochemistry of Santosh Medical College, Ghaziabad, UP, India, from June 2021 to February 2022. In this study, 200 average pregnant women were enrolled. The thyroid profile was estimated using the ELISA method, and the lipid profile was measured using the enzymatic kit method. All data were expressed as means and standard deviations, and SPSS version 17 was used for statistical analysis.

Results: This observational study observed that the mean T3, T4, and TSH levels increased significantly in the second trimester compared to the first trimester. In contrast, the mean value of T3, T4, and TSH decreased in the third trimester as compared to the second trimester. The mean levels of total cholesterol, triglyceride, and LDL-cholesterol increased significantly, while the mean value of HDL-cholesterol decreased significantly in the second and third trimesters when compared to the first trimester.

Conclusion: This study demonstrated abnormal lipid and thyroid metabolism. Changes in thyroid profile may be associated with adverse obstetric outcomes. The altered lipid parameters, mainly High TG and low HDL-C concentrations, may promote vascular dysfunction and oxidative stress.

Keywords: Pregnancy, thyroid hormones, triglycerides, trimester

Introduction

Pregnancy is known as the period of gestation. During this period, new life grows inside a female's uterus. Pregnancy causes alterations in internal and external physiological status of a woman. Many external physiological changes are observed in this time, such as changes in blood values, which may appear pathological if seen in non-pregnant women. However, these pregnancy-related changes are beneficial for the development and growth of the fetus because the altered physiology greatly affects and helps in supplying proper nutrients and protection to the developing fetus until the time of delivery.[1] These changes are also contributed by various endocrinal changes in pregnancy, in which the thyroid gland plays a critical role in regulating the thyroid hormones synthesis necessary for the infant's brain and nervous system development. Since the fetus completely depends on the mother's thyroid hormone throughout the first trimester, the mother's thyroid gland is enlarged to produce more thyroid hormones. Thyroid gland dysfunction is also common during pregnancy. If it remains untreated, it may trigger adverse effects on the pregnancy and fetal outcomes.[2]

During pregnancy, the mother physically changes and increased blood levels of progesterone, estrogens, and pancreatic beta-cell hyperplasia change the maternal metabolic milieu. A significant part of the lipid profile's disturbance is due to the insulin resistance and ovaries-estrogens in women. So, identification of these disorders and their treatments are necessary to prevent complications related to pregnancy. Changes in thyroid hormones and in TSH may be a factor in a disrupted lipid profile, particularly in the third trimester. Many studies have examined the alterations in pregnant women's lipid profile, T3, T4, and TSH during the three stages of pregnancy to ascertain why these characteristics change during pregnancy.[3] Reports on the relationship between dyslipidemia, pregnancy outcomes, and thyroid gland malfunction have resulted in conflicting results, with the first trimester receives less attention as most studies tend to concentrate on the late stages of pregnancy. Hence, this study aimed to determine serum lipid level and thyroid profile in all trimesters of normal pregnancy.

Methods

This study was conducted at the Department of Biochemistry of Santosh Medical College Ghaziabad, Uttar Pradesh, India from June 2021 to February 2022. Institutional ethical committee clearance [SU/2020/536(50)] and inform consent from patient were obtained prior to the study. This study included 200 pregnant healthy women of 21–32 years of age. Women on hormonal therapy, steroid therapy, already diagnosed thyroid patients, having abnormal liver function and kidney function, and experiencing acute or chronic inflammatory diseases were excluded. Blood samples were collected after 8-12 hours of fasting, three times from the women (in first, second and third trimester) in fluoride/plain vials under all aseptic precautions. Plasma/serum were separated and all parameters were measured on the same day as the collection. Fasting blood glucose, total cholesterol, HDL-cholesterol, triglyceride, and LDL-cholesterol were measured by enzymatic kit method using a fully automatic analyzer (Beckman Coulter- AU-480). Serum T3, T4 and TSH were tested by commercially available ELISA kits using Beckman Coulter-Chemistry Analyzer Access-2. The parameters of blood glucose and lipid were measured using a fully automated analyzer (Beckman Coulter –AU-480), while an automated analyzer (Chemistry Analyzer-Access-2's) was used to measure the thyroid profile. Statistical Package for Social Sciences (SPSS) version 17 was used for statistical analyses and the statistical test results were summarized as means and standard deviations in several tables. The confidence intervals for each of the presented p-values were determined at the 95% level with $p < 0.05$ was considered significant.

Results

This study involved 200 normal pregnant women above 20 year of age. The mean value of the T3 and TSH increased in the 2nd and 3rd trimester of pregnancy as compared to the 1st trimester, and it was statistically significant. The mean value of T4 increased in the 2nd trimester but decreased in the 3rd trimester, and it was statistically significant. The mean values of total cholesterol, triglyceride (TG), and LDL-cholesterol were found to be increased

Table 1 Comparison of Biochemical Parameters in 1st and 2nd Trimester of Pregnancy (n=200)

Variable	1st Trimester	2nd Trimester	p-value
T3 (ng/mL)	1.07 ± 0.15	1.19 ± 0.27	0.038
T4 (µg/mL)	5.54 ± 2.06	7.56 ± 2.11	0.004
TSH (µlU/mL)	1.76 ± 0.74	3.97 ± 1.96	<0.0001
Fasting blood Glucose (mg/dL)	81.03 ± 11.89	90.43 ± 15.42	0.01
Total Cholesterol (mg/dL)	155.73 ± 27.61	171.8 ± 30.11	0.035
HDL-cholesterol (mg/dL)	49.67 ± 5.05	46.20 ± 5.80	0.016
Triglyceride (mg/dL)	154.83 ± 26.02	186.30 ± 32.38	0.0001
LDL-cholesterol (mg/dL)	72.10 ± 8.43	85.23 ± 11.23	<0.0001

*p-value less than 0.05 is considered statistically significant

Table 2 Comparison of Biochemical Parameters in 1st and 3rd trimester of Pregnancy (n=200)

Variable	1st Trimester	3rd Trimester	p-value
T3 (ng/mL)	1.07 ± 0.15	1.32 ± 0.17	<0.0001
T4 (µg/mL)	5.54 ± 2.06	6.58 ± 1.06	=0.017
TSH (µlU/mL)	1.76 ± 0.74	4.87 ± 1.45	<0.0001
Fasting blood Glucose (mg/dL)	81.03 ± 11.89	97.12 ± 8.78	<0.0001
Total Cholesterol (mg/dL)	155.73 ± 27.61	194.10 ± 44.33	=0.0002
HDL-cholesterol (mg/dL)	49.67 ± 5.05	41.87 ± 4.50	=0.0001
Triglyceride (mg/dL)	154.83 ± 26.02	208.7 ± 47.71	<0.0001
LDL-cholesterol (mg/dL)	72.10 ± 8.43	111.45 ± 18.91	<0.0001

*p-value less than 0.05 considered as statistically significant

significantly in the 2nd and 3rd trimester when compared to the values in the 1st trimester and the mean value of HDL-cholesterol decreased significantly in the 2nd and 3rd trimester when compared to 1st trimester (Table 1 and 2).

Differences in all the studied parameters in the 2nd and 3rd trimester were statistically significant (Table 3).

Discussion

Pregnancy is one of the most vital phases in the life of a woman. During pregnancy, various changes in the hormonal, vascular, metabolical, immunological, and psychological conditions are seen, which are beneficial to nurture the developing fetus and also affect the levels of normal biochemical parameters while others may mimic symptoms of medical diseases. In the current study, a total of 200 pregnant women were recruited and were followed up in all three trimesters. The age range of the participants was from 20 to 30 years old, which is line with a previous study that stated that the most probable fertile years and reproductive age of a woman is 20–30 years, with the best reproductive years are in the 20s.[4] Lipid profile is significantly affected by the endogenous sex hormones of females. Endocrine changes during pregnancy, e.g., rising levels of estrogen, progesterone, and cortisol, will cause lipogenesis and fat accumulation associated with hyperphagia. Pregnancy-related increases in lipid synthesis are required as an energy source to meet the metabolic requirements of both the mother and the fetus.[4] In the present study, the mean value of total cholesterol, triglyceride, and LDL-cholesterol in the first, second, and third trimesters of pregnancy were found to be increased significantly. These results are line with the findings of previous studies that reported gradual increases of lipid fractions in all three stages of pregnancy.[4, 5] Another related

Table 3 Comparison of Biochemical Parameters in 2nd and 3rd Trimester of Pregnancy (n=200)

Variable	2nd Trimester	3rd Trimester	p-value
T3 (ng/mL)	1.19 ± 0.27	1.32 ± 0.17	0.295
T4 (µg/mL)	7.56 ± 2.11	6.58 ± 1.06	0.03
TSH (µlU/mL)	3.97 ± 1.96	4.87 ± 1.45	0.047
Fasting blood Glucose (mg/dL)	90.43 ± 15.42	97.12 ± 8.78	0.04
Total Cholesterol (mg/dL)	171.8 ± 30.11	194.10 ± 44.33	0.026
HDL-cholesterol (mg/dL)	46.20 ± 5.80	41.87 ± 4.50	0.002
Triglyceride (mg/dL)	186.30 ± 32.38	208.7 ± 47.71	0.037
LDL-cholesterol (mg/dL)	85.23 ± 11.23	111.45 ± 18.91	<0.0001

*p-value less than 0.05 is considered statistically significant

study reported the gradual increases in the mean values of cholesterol and triglycerides in the second and third trimesters which is similar to this study.[4] In their study, Kumari *et al*. demonstrated a significant increase in cholesterol during all three trimesters.[6] Another study also showed that TC and TG concentrations rise up in late pregnancy when compared to non-pregnant women.[7] Evidence also suggests that blood lipids return to pre-pregnancy levels after delivery, which implies that the elevated serum lipids may play a significant role in fetal development. However, a high cholesterol level during pregnancy may lead to pregnancy-induced hypertension, a cardiovascular risk which can threaten the life of both the mother and child. On the other hand, a low cholesterol level can lead to early and premature labor and low birth weight.[8]

A previous study also reported the presence of hypertriglyceridemia in pregnancy and gradual increase in TG level in all trimesters, and also found a significant difference in the TG level when compared to non-pregnant women.[9] To explain this phenomenon, one study stated that due to the high energy demand in pregnancy, the energy production to meet the maternal need of fuel is switched from carbohydrate metabolism to lipid metabolism. Therefore, increased lipid deposition and decreased lipolysis are observed in early pregnancy.[4] Another explanation for the rise in triglyceride and other lipid components during normal pregnancy seen in parallel with the rise in gestational age is the rise in estrogen and progesterone levels during gestation.[4,9]

Decreased HDL-C was found in this study. A low HDL-C level is said to increase the risk for coronary heart disease, and many pregnancies have mixed outcomes. It is thought that the fall in serum HDL-C during the third trimester of a typical pregnancy may be a potential risk factor for atherosclerosis to occur. Another explanation of increased LDL-C is the high levels of progesterone and estrogen during pregnancy.[4] The higher LDL-c during pregnancy may be used to identify women who may experience atherogenic alterations in the future.[10] Similar pattern of variations in lipid profile is also presented by other previous studies just like in the present study.[4,10] A previous study stated that there may be two factors that increase the TG level; first, increased activities of hepatic lipase which is responsible for the synthesis of hepatic triglycerides and, second, reduced lipoprotein lipase activity which results in a reduction in the catabolism of adipose tissues.[10] During pregnancy, significant changes are also seen in thyroid hormone physiology and thyroid gland anatomy.[10]

In the present study, an elevated pattern in TSH level is observed in the first, second and third phase of pregnancy. However, despite being observed in a normal limit, increasing TSH value indicates the risk for developing hypothyroidism. To support this Yoganathan *et al.*, studied the thyroid status in pregnant women and found an increase in the TSH value of pregnant women with hypothyroidism with a positive correlation.[11] Another study of Mehta *et al*.,[12] reported increased TSH concentration in the third trimester compared with the second trimester. This study stated that increased TSH value may be considered as a risk factor for decreased neurological development and preterm birth.[13]In the present study, the mean T3 level increases significantly in the 2nd and 3rd trimester as compared to the 1st trimester but it is still in the normal range. The T4 level increases in the 2nd trimester as compared to the 1st trimester, but decreases in the 3rd trimester as compared to the 2nd trimester. Iodine is organized and oxidized by the thyroid peroxidase enzyme, which also produces the fT4 and fT3 hormones.[14] A glycoprotein called thyroglobulin serves as a substrate for the production and storage of thyroid hormones.[15] Hypothyroidism is the outcome of these antibodies in autoimmune thyroid diseases. Thyroid autoimmunity is linked to recurrent miscarriage, which is probably brought on by generalized immune system activation and transplacental transfer of antibodies that result in fetal rejection.[16]

Women have a high risk for experiencing thyroid dysfunction, including hypothyroidsm, which is linked to increased lipid fractions, i.e. TC, LDL, and TG, and decreased HDL-C. Elevated LDL-C levels result in increased oxidation of LDL-C, which is a high risk factor of atherosclerosis. Hypothyroidism is also linked with a decreased activity of lipoprotein lipase that leads to decreased clearance of TG-rich lipoprotein.[17] In line with this study, Sangeeta *et al*. also reported elevated levels of TC, LDL-C, and TG with an elevated level of TSH. Decreased HDL-C is also linked to hypothyroidism due to increased transfer of cholesterol esters from HDL to VLDL, mediated through CETP, which increases the HDL catabolism.[18]

Both thyroid profile and lipid profile have a vital role in pregnancy. In early pregnancy, thyroid impairment is common and prevalent and is associated with dyslipidemia. During

pregnancy, a poor metabolic phenotype is associated with thyroid dysfunction. The effect of body weight on the association of lipid parameters and thyroid hormones are not well studied yet. A woman's physiological weight increase during pregnancy may have an impact on her lipid profile and thyroid hormone levels. A bigger sample size and prospective methodological investigations in different centers are required in the future to examine the association of thyroid profile with lipid profile with a larger sample size, as the current study was only done in one hospital, thus becomes the limitation of this study.

In the present study, it was observed that T3, T4 and TSH levels are raised. Obstetric problems can result from aberrant thyroid hormones. Thyroid disorders have an impact on both the mother and the fetus. Early in pregnancy, maternal thyroid hormones and TSH are linked to dyslipidemia and a number of unfavorable pregnancy outcomes. Total cholesterol, triglycerides, and LDL are shown to be significantly higher across all lipid profile indicators as a result of endothelial dysfunction. Conventional maternal thyroid in early pregnancy may help improve the lipid levels and decrease several possible adverse pregnancy outcomes.

References

1. Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience. 2017;342:68–100. doi:10.1016/j.neuroscience.2015.09.070.
2. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. Cardiovasc J Afr. 2016;27(2):89–94. doi:10.5830/CVJA-2016-021.
3. Jiffri EH. Relationship between lipid profile blood and thyroid hormones in patient with type 2 diabetes mellitus. Adv Obes Weight Manag Control. 2017;6(6):178–82. doi:10.15406/aowmc.2017.06.00176
4. Abdullah TH, Baqi HR, Karim SH, Ghafor DA. Association of lipid profile with body mass index in Public Employees in Halabja City, Kurdistan Region of Iraq. Polytechnic Journal 2020;30(10):71–80. doi: 10.25156/ptj.v10n2y2020.pp71-80
5. Sonagra AD, Shylaja TV, Deba Z, Makandar A. Study of serum lipid profile in normal pregnancy. International Journal of Biotechnology and Biochemistry 2017;13(2):175–82.
6. Kumari K, Sharan S, Kumar R. Assessment of changes in lipid profile of pregnant women during periods of gestation and post partum in Chotanagpur – a descriptive study. International Journal of Contemporary Medical Research 2018;5(5):E4-E7. doi: http://dx.doi.org/10.21276/ijcmr.2018.5.5.14
7. Parveen S , Zaman I, Noor N , Moin S , Ali SM. Maternal lipid profile and its impact on pregnancy outcome. J South Asian Feder Obs Gynae 2022;14(3):302–6. doi: 10.5005/jp-journals-10006-2051
8. Chen Q, Chen H, Xi F, Sagnelli M, Zhao B, Chen Y, et al. Association between maternal blood lipids levels during pregnancy and risk of small-for-gestational-age infants. Sci Rep. 2020;10(1):19865. doi:10.1038/s41598-020-76845-1
9. Cibickova L, Schovanek J, Karasek D. Changes in serum lipid levels during pregnancy in women with gestational diabetes. A narrative review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2021;165(1):8–12. doi:10.5507/bp.2021.009
10. Pusukuru R, Shenoi AS, Kyada PK, Ghodke B, Mehta V, Bhuta K, et al. Evaluation of lipid profile in second and third trimester of pregnancy. J Clin Diagn Res. 2016;10(3):QC12-QC16. doi:10.7860/JCDR/2016/17598.7436
11. Yoganathan T, Hettiarachchi M, Arasaratnam V, Liyanage C. Maternal iodine status and the thyroid function of pregnant mothers and their neonates in Jaffna District of Sri Lanka. Indian J Endocr Metab 2015;19:817–23. doi:10.4103/2230-8210.167563
12. Mehta V, Pusukuru R, Ghodke B. Association of Thyroid Stimulating Hormone and Lipid Profile in Pregnancy. J Med Res Innov. 2017;1(2):AU1–AU6. doi : 10.15419/jmri.50
13. Devi RV, Oinam S, Bishwalata RK, Singh NI, Singh TR. A study of association between lipid profile and thyroid hormones in pregnancy. IOSR J Dental Med Sci (IOSRJDMS) 2018;17(9):55–60. doi: 10.9790/0853-1709015560
14. Hannoush ZC, Weiss RE. Defects of thyroid hormone synthesis and action. Endocrinol

Metab Clin North Am. 2017;46(2):375–88. doi:10.1016/j.ecl.2017.01.005
15. TG thyroglobulin [Homo sapians (human)]-Gene- NCBI. [cited 2019-09-16]. Available from: https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=7038.
16. Lata K, Dutta P, Sridhar S, Rohilla M, Srinivasan A, Prashad GRV, et al. Thyroid autoimmunity and obstetric outcomes in women with recurrent miscarriage: a case–control study. Endocr Connect. 2013;2(2):118–24. doi:10.1530/EC-13-0012
17. Duntas LH, Brenta G. A Renewed focus on the association between thyroid hormones and lipid metabolism. front endocrinol (Lausanne). 2018;9:511. doi:10.3389/fendo.2018.00511
18. Sangeeta N, Singh AK, Devi P , Singh RKR, Chubalemla L, Abhishek D, et al. Lipid Profile in thyroid dysfunction patients. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 2016;15(12):39–43. doi: 10.9790/0853-1512113943

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Original Article

Outcome of Posterior Cruciate Ligament Avulsion Fractures from Tibial Attachment Treated by Open Reduction and Internal Fixation

Shouryashil V. Khambalkar, Tanish C. Patil, Jaydeep K. Patil, Kapil R. Ghorpade, Nagesh Naik

Department of Orthopedics, Prakash Institute of Medical Sciences and Research Centre, Islampur, Sangli, India

Article History

Received: July 21, 2023
Accepted: October 02, 2023
Published: October 30, 2023

DOI: 10.15850/ijihs.v11n2.3471
IJIHS. 2023;11(2):85–91

Correspondence:
Kapil R Ghorpade,
Department of Orthopaedics,
Prakash Institute of Medical Sciences and Research Centre,
Islampur, Sangli. India.
Email: drkapilghorpade@gmail.com

Abstract

Objective: To study the clinical profile and treatment outcome of mucormycosis associated with the second wave of COVID-19 pandemic.

Methods: An observational study was conducted in a tertiary care center over a period of 12 months, including a 6-month post treatment follow up. Study included all COVID positive patients with a clinical and radiological evidence of rhino-orbito-cerebral mucormycosis during the second wave of COVID-19. All patients underwent further diagnostic workup and confirmed cases underwent surgical debridement and Amphotericin B was started.

Results: A total of 59 patients presented with mucormycosis with the mean age being 52.7 years and unilateral facial and orbital edema as the most common symptoms (28.8%). All were diabetic with HbA1c >7 in 54.2%. The mean duration of presentation was 20.7±7.9 days from the onset of COVID-19 infection. Unilateral involvement of the paranasal sinuses was the most common finding in MRI. Early administration of Amphotericin B with prompt surgical debridement was performed in all cases. Orbital exenteration was conducted in nine patients for better fungal load clearance. Patients showed a good response to surgical debridement and prompt medical treatment, with a mortality rate of 27%.

Conclusion: COVID-19 associated mucormycosis is difficult to treat and often presents in late stage. Uncontrolled diabetes, immunocompromised state, and steroid-induced immunosuppression were important risk factors. A close surveillance for early identification and initiation of treatment is mandatory. Repeated surgical debridement to clear the dead tissue is effective to control fungal load.

Keywords: Amphotericin B, COVID-19, invasive fungal sinusitis, mucormycosis

Introduction

Posterior Cruciate Ligament (PCL) is stronger than the anterior cruciate ligament (ACL) and plays a crucial role in stabilizing the knee.[1] It acts as the primary restraint against posterior tibial displacement and works in conjunction with the anterior cruciate ligament (ACL) to regulate the external rotation of the knee during extension. PCL injuries are estimated to account for approximately 20% of knee ligament injuries, with higher incidence rates observed in cases of high-energy trauma, such as motorcycle and car accidents, and in contact sports among athletes.[2] With increasing involvement of youth in sports activities there is increased incidence of these fractures. The other common mechanism of injury to the posterior cruciate ligament is caused by the application of a force to the proximal tibia anteriorly when the knee is flexed. The functional impairment PCL

injuries may range from mild discomfort to severe functional impairment.[3] In cases with PCL avulsion fracture, a history of posteriorly directed force on flexed knee or history of fall on flexed knee may be present. The physical examination may show the presence of joint swelling, hemarthrosis, or contusion over the anterior tibia. Diagnosis may be confirmed on the basis of anteroposterior and lateral X-Ray of the affected knee which may show presence of bone discontinuity at the posterior tibial articular surface.[4] Computed tomography and MRI may also help in further evaluation of fracture, as well as identifying accompanying injuries such as meniscal tears or soft tissue involvement. Computed Tomography and MRI have a high sensitivity for the diagnosis of PCL avulsion fracture. PCL avulsion fractures usually involve tibial attachment and, when this occurs, it is essential to promptly diagnose and initiate the appropriate management to optimize the clinical and functional outcomes of the patients.[5] Once diagnosed, the treatment is usually surgical. Unlike in patients with isolated PCL injuries where the repair is usually deferred, cases with avulsion fracture needs prompt surgical interventions in order to prevent complications that may take the forms of malunion and non-union. The repair for these fractures can be done arthroscopically or by open reduction.[6] In developing countries, arthroscopic surgeries are not commonly done due to the expensive cost and high requirements of facility; in addition, specific expertise is also required to perform arthroscopic repairs, which are not available except in urban areas. Thus, open reduction and internal fixation using screws remain one of the most common surgeries in rural and semi urban areas for PCL avulsion fractures. Various materials that can be used for internal fixation include, among others, lag screws, suture anchors, steel wires, and straddle nails, as well as a well-designed rehabilitation program as an essential part of the management of these patients.[7] The clinical and functional outcomes of patients with PCL fractures treated by ORIF have been a subject of interest for researchers and clinicians alike. Understanding the long-term outcomes of open reduction and internal fixation for PCL avulsion fractures is crucial for guiding treatment decisions, optimizing surgical techniques, and improving patient care.[8] Numerous studies have investigated the efficacy of this surgical technique and its impact on patients' quality of life and functional recovery.[9] However, many of these studies defined the outcomes on the basis of patients' subjective assessment of functional recovery. In this study, multiple objective scores to measure functional outcomes. This study aimed an observational study to analyze clinical and functional outcomes of posterior cruciate ligament avulsion fractures from tibial attachment treated by open reduction and internal fixation.

Methods

This study was conducted at the Department of Orthopedics, Prakash Institute of Medical Sciences and Research Centre, Islampur, Sangli. India. The duration of study was 2 years, starting from April 2021 to March 2023. In this study, 40 adult patients of either gender with PCL avulsion fractures were included on the basis of a predefined inclusion and exclusion criteria. Using the OPENEPI software version 3, by referring to a pilot study done on the PCL Avulsion fractures and assuming 90% power and 95% confidence interval, the sample size was determined to be adequate if it was more than 35 patients; thus, 40 patients were included in this study. The inclusion criteria was adult patients with isolated PCL avulsion fracture as diagnosed by imaging results (X-Ray, Computerized Tomography, and Magnetic resonance imaging) where the PCL fragment was displaced more than 5 mm and were presented within 4 weeks of injury. Patients who refused to participate or those who were presented after 4 weeks of injury, as well as patients with PCL fragment displacement of less than 5 mm were excluded from the study. Patients with musculoskeletal conditions likely to affect the outcomes of the assessment, such as those having osteoarthritis, rheumatoid or psoriatic arthritis and those with multiple fractures, were also excluded. A detailed history was taken from all patients with respect to type of trauma and duration since injury. A thorough clinical examination was done by a senior orthopedician in all the cases. Drawer test was performed to make the preliminary diagnosis of PCL injury. Imaging was done in the form of anteroposterior and lateral view radiographs of the affected knee. In selected cases, 3D computed tomography (CT) was done. Since X-ray and CT has low sensitivity for assessment of soft tissue damage and injury, magnetic resonance imaging was done in selected cases. Preanesthetic evaluation was performed in all cases. Routine investigations, such as complete hemogram, renal function

tests, bleeding and clotting time, and Hepatitis B and HIV ELISA tests were done in all cases. In cases involving patients above 45 years of age, physician's opinion regarding fitness for the surgery was sought. All patients were treated by open reduction and internal fixation of avulsion fracture.

During the surgical procedure, patients were given spinal anesthesia and placed in a prone position with the affected limb flexed. An inverted L-shaped incision was made, exposing the PCL tibial attachment through the interval between the medial gastrocnemius and semimembranosus, and the posterior knee capsule was incised to reveal the avulsed PCL tibial insertion fragment. The fracture hematoma was removed, and in cases of old injuries, any fibrous tissue was debrided from the avulsed fragment or its bed. Under the C-arm guidance, the fractured fragment was visualized and repositioned over the posterior tibial plateau and sutured at the osteo-ligamentous junction. Then, a long, thin guide wire was passed from the center of the fragment, directed from posterior to anterior through the proximal tibia, with the knee in flexion, ensuring it made a 45-degree angle to the posterior surface of the tibia. After safely drilling over the guide wire and measuring the length, a 4 mm cannulated cancellous screw with a washer was later fixed in place. The fragment was reduced under direct vision to its bed (facilitated by slight knee flexion), gently held in place using a spike pusher, and provisionally fixed with a K-wire. The position of the reduced fragment was checked by fluoroscopy. Postoperative above knee slab given with padded support to superior part of calf to keep knee in anterior drawer position. Quadriceps exercises and non-weight bearing mobilization was started from next day. Suture removal was performed after 15 days. Passive knee bending started after 1 month with toe touch weight bearing. Full weight bearing started after full range of movements achieved after 6-8 weeks. Although full routine activities were allowed after 3 months, participation in contact sports was avoided till 9 – 12 months according to rehabilitation and muscle strength recovery. The patients were followed up every monthly for 3 months and, after that, every 3 months for 12 months. At every follow up visit, patient clinical and functional assessments were done using the Lysholm knee score (LKS) and Knee Society Score[10]. Qualitative data were represented in percentages and quantitative data were represented as mean with standard deviation. The statistical analysis was done using the SSPS 22.0 software and a p-value of less than 0.05 was taken as statistically significant.

Results

Fourty cases of posterior cruciate ligament avulsion fractures from tibial attachment that were treated by open reduction and internal fixation were included in this study, of which there were 34 (75 %) males and 6 (15%) females with an M: F ratio of 1:0.17. Twenty-six (65 %) of the participants had their right side affected, whereas the remaining 14 (35 %) of the cases had left sided PCL avulsion fracture. The analysis of the age group of the patients showed that the most common affected age group was between 31-40 years (57.5%), followed by 41-50 years (27.50%). The mean age of affected patients was found to be 37.3 +/- 7.34 years (Table 1).

Out of 40 patients, 29 (72.50%) sustained fracture secondary to road traffic accidents while 7 (17.50%) had sports-related injuries. In 4 (10%) patients fracture was secondary to falls. The majority of the patients (52.50%) were presented within 7 days of sustaining injury, while 19 (47.50%) were presented between 8 days to 4 weeks after injury (Table 2).

Functional assessments at the time of each follow up was performed using the Lysholm score and knee society score. At the time of presentation, the mean Lysholm score was found to be 4.5 +/- 2.8, with a gradual improvement with each follow up and reaching 72.8 +/- 9.2 at 3 months, and 98.2 +/- 10.1 at the time of final follow up. This difference between the initial score and final score was statistically highly significant (Fig. 1).

The functional assessment of the knee was also done by knee society score. At the time of presentation, the mean knee society score was

Table 1 Age Distribution of the Studied Cases

Age	No of cases	Percentage
18-30 years	3	7.50%
31-40 years	23	57.50%
41-50 years	11	27.50%
Above 50 years	3	7.50%
Total	40	100 %
Mean Age	37.3 +/- 7.34 years	

Table 2 Mechanism of Injury and Duration Since Injury

Mechanism and Duration of Injury		Number of Cases	Percentage
Mechanism of Injury	Road Traffic Accidents	29	72.50%
	Sports Injuries	7	17.50%
	Falls	4	10.00%
Duration Since Injury	Within 24 hours	9	22.50%
	2–7 days	12	30.00%
	8 days–2 weeks	10	25.00%
	15 days–4 weeks	9	22.50%

34.16 +/- 12.34, which gradually improved to 82.76 +/- 10.36 at 6 months, and at the time of final follow up, the mean knee society score was 92.34 +/- 8.12. In addition, there was a significant improvement in cases as assessed by knee society score ($p<0.0001$). At the time of presentation, all patients were having moderate to severe pain. The mean VAS score at the time of presentation was 6.3 +/- 2.62. In the postoperative period, the pain reduced signifciantly over a period of weeks to months. At the time of final follow up at 12 months,

Table 3 Mean Knee Society Score at Presentation and During Follow Up

Comparison of Knee Society and VAS Scores		Mean +/- Std Deviation	P Value
Knee Society Score	At Presentation	26.34 +/- 9.98	P < 0.0001 (Paired t-test) Highly significant
	At 1 Month	42.16 +/- 12.34	
	At 2 Months	46.78 +/- 14.62	
	At 3 Months	64.38 +/- 14.02	
	At 6 months	78.64 +/- 12.16	
	At 9 months	82.76 +/- 10.36	
	Final Follow Up (1 year)	88.20 +/- 8.12	
VAS Score	At Presentation	6.36 +/- 2.64	P < 0.0001 (Paired t-test) Highly significant
	At 1 Month	3.94+/- 1.84	
	At 2 Months	3.12 +/- 1.74	
	At 3 Months	2.68 +/- 1.36	
	At 6 months	2.12 +/- 1.22	
	At 9 months	1.80 +/- 0.92	
	Final Follow Up (1 year)	1.24 +/ 0.72	

Table 4 Patient Outcomes by Knee Society Score

Outcome (KSS score)	Number of patients	Percentage
Excellent (80–100)	29	72.50%
Good (70–79)	6	15.00%
Fair (60–69)	4	10.00%
Poor (<60)	1	2.50%

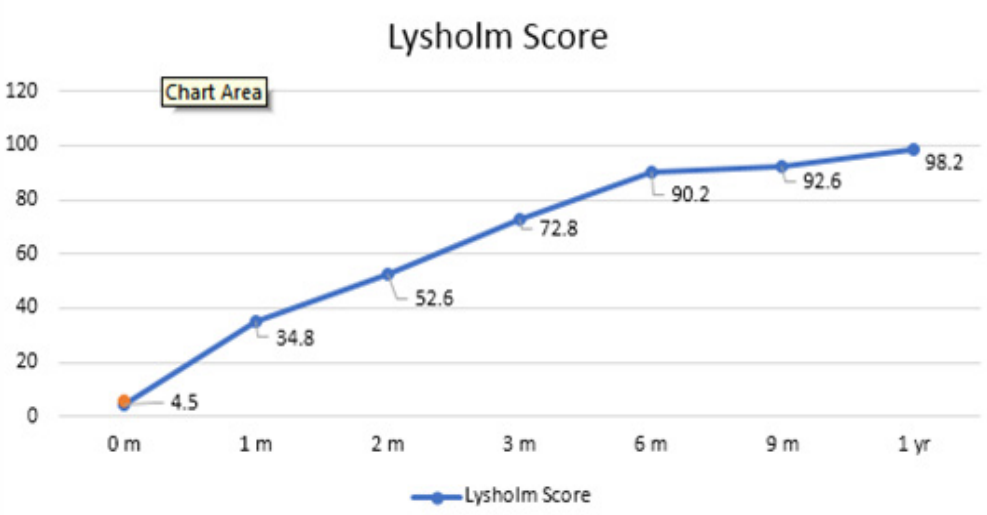

Fig. 1 Mean Lysholm Score at Presentation and During Follow Up

there was a significant reduction in the VAS scores. At the time of the final follow up, the mean VAS score was found to be 1.24 +/- 0.72 ($p<0.0001$) (Table 3).

The final functional outcome as assessed by the Knee society score showed that out of 40 cases, 29 (72.50%) cases had an excellent outcome whereas 6 (15%) and 4 (10%) patients had a fair outcome. Only 1 patient (2.50%) had a KSS below 60, suggestive of poor outcome (Table 4).

The analysis of the patients on the basis of complications showed that out of 40 patients, 32 (80%) patients did not have experience any complications. Five (12.5%) patients had residual intermittent pain, 2 (5%) patients had wound infections, which was successfully treated by oral antibiotics and local wound care. Only 1 (2.5%) patient developed residual joint instability as evidenced by the drawer test (Fig. 2).

Discussion

Posterior cruciate ligament injuries usually result from road traffic accidents or contact sports injuries. Unlike in cases of isolated PCL tears where the management remains controversial, guidelines for PCL avulsion fractures is unanimous, and open reduction and internal fixation remains the preferable line of management and conservative management

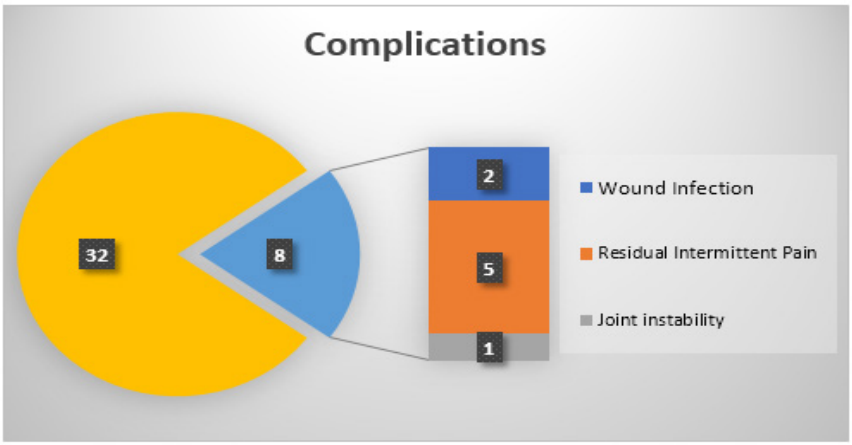

Fig. 2 Complications in the Studied Cases

is not desirable given the high chances of non-union or malunion, which may further destabilize the affected knee.[11] In this study, there was a significant male preponderance in cases of PCL avulsion fractures. Male preponderance is almost universal across studies because of predominant involvement of males in road traffic accidents and contact sports, which remains common causes of PCL avulsion fractures. Bali *et al.*[12], in their study to analyze the outcome of posterior cruciate ligament (PCL) avulsion fractures of tibia with open reduction and internal fixation, involved 42 patients (30 males and 12 females), with a median age of 26 years (range: 14–53 years) who underwent ORIF through a modified, posterior approach for PCL fossa avulsion fractures assessed after a median follow up of 18 months (range 10-42 months). In 30 patients, surgeries were performed within three weeks of injury. Their study showed a significant male preponderance with an M:F ratio of 1:0.4. Similarly, male preponderance was also reported by the authors such as Khatri *et al.*[13] and Fan *et al.*[14] The mean age of studied cases in the study was found to be 37.3 +/- 7.34 years. Twenty-nine (72.50%) patients was found to experience fracture secondary to road traffic accidents while seven (17.50%) patients had sports related injuries. In four (10%) patients, fracture was secondary to falls. In the western world, most of the PCL injuries are results of a type of injury popularly known as dashboard injuries where the injury occurs in sitting position and sudden abrupt force is applied on the anterior aspect of tibia. However, in developing world, including in India, PCL injuries are usually results of road traffic accidents involving bikes. Chen *et al.*[15] conducted a study to investigate the feasibility and clinical efficacy of using a toothed plate and hollow lag screw in the surgical treatment of posterior cruciate ligament (PCL) avulsion fractures of the tibia, which was a retrospective study of patients with PCL avulsion fractures of the tibia caused by road traffic accidents (n=9), sports-related injuries (n=6), falls (n=5), and machinery-related injuries (n=1) involving twenty patients who are presented with fresh fractures and one with an old fracture. These patients (13 men, eight women) had a mean age of 41.5 (range 19–72) years. Their findings were similar with respect to cause of avulsion fracture; however, the mean age of patients in their study was slightly higher. Similar findings were also reported by authors such as Owesen *et al.*[16] and Sanders *et al.*[17] In those studies, all patients were treated by open reduction and internal fixation of avulsed part of tibia. Patients were followed up for 1 year. During follow up visits x-rays were taken to assess the union. Also, the functional assessment was done using Lysholm score and knee society score. Both Lysholm and knee society score were found to gradually improve over the period of follow up and there was a significant functional improvement in both mean Lysholm and knee society scores when compared from presentation to the previous follow up visit. The outcome assessment by KSS (Knee society score) showed that out of 40 cases 29 (72.50%) cases had an excellent outcome whereas 6 (15%) and 4 (10%) patients had fair outcome. Only one patient (2.50%) had a KSS below 60, suggestive of a poor outcome.

Joshi *et al.*[18] also performed a similar study of open reduction and internal fixation using cannulated cancellous screws in 14 patients (mean age, 33.9 years) with isolated PCL avulsion injuries. At the time of the final follow up the authors found that the Lysholm functional score was excellent in 11 patients, good in 2 patients, and fair in 1 patient with an average score of 97±7.6. Similar findings were also reported by the authors such as Wu *et al.*[19] and Khalifa *et al.*[20] Being a purely observational study, this study has its inherent biases. A randomized control trial would be needed to further substantiate the outcome of this observational study. A prolonged follow up observation will also be helpful in knowing long term complications of this treatment approach.

In conclusion, patients with posterior cruciate ligament avulsion fracture treated by open reduction and internal fixation combined with quadriceps exercises in post-operative period were found to have excellent results in terms of functional outcomes.

References

1. Zlotnicki JP, Naendrup JH, Ferrer GA, Debski RE. Basic biomechanic principles of knee instability. Curr Rev Musculoskelet Med. 2016;9(2):114–22. doi:10.1007/s12178-016-9329–8.
2. Pache S, Aman ZS, Kennedy M, Nakama GY, Moatshe G, Ziegler C, et al. Posterior cruciate ligament: current concepts review. Arch Bone Jt Surg. 2018;6(1):8–18. doi:10.22038/

abjs.2017.25851.1686
3. Pierce CM, O'Brien L, Griffin LW, Laprade RF. Posterior cruciate ligament tears: functional and postoperative rehabilitation. Knee Surg Sports Traumatol Arthrosc. 2013;21(5):1071–84. doi:10.1007/s00167-012-1970-1
4. Ridley U, Ridley L. Imaging of the knee: Common acute presentations to general practice. Aust J Gen Pract. 2020;49(6):344–9. doi:10.31128/AJGP-10-19-5120
5. Hooper PO 3rd, Silko C, Malcolm TL, Farrow LD. Management of posterior cruciate ligament tibial avulsion injuries: a systematic review. Am J Sports Med. 2018; 46(3):734–42. doi:10.1177/0363546517701911
6. Sundararajan SR, Joseph JB, Ramakanth R, Jha AK, Rajasekaran S. Arthroscopic reduction and internal fixation (ARIF) versus open reduction internal fixation (ORIF) to elucidate the difference for tibial side PCL avulsion fixation: a randomized controlled trial (RCT). Knee Surg Sports Traumatol Arthrosc. 2021;29(4):1251–7. doi:10.1007/s00167-020-06144-9
7. Simhal RK, Bovich M, Bahrun EA, Dreese JC. Postoperative rehabilitation of posterior cruciate ligament surgery: a systematic review. Sports Med Arthrosc Rev. 2021;29(2):81–7. doi:10.1097/JSA.0000000000000307
8. Vishwakarma NS, Gali JC, Gali JC, LaPrade RF. The outcomes of posterior cruciate ligament tibial avulsion fixation with a screw using a dual posteromedial portal technique. Acta Ortop Bras. 2022;30(spe2):e246988. doi:10.1590/1413-785220223002e246988
9. Katsman A, Strauss EJ, Campbell KA, Alaia MJ. Posterior cruciate ligament avulsion fractures. Curr Rev Musculoskelet Med. 2018;11(3):503–9. doi:10.1007/s12178-018-9491-2
10. Culliton SE, Bryant DM, MacDonald SJ, Hibbert KM, Chesworth BM. Validity and internal consistency of the new knee society knee scoring system. Clin Orthop Relat Res. 2018;476(1):77–84. doi:10.1007/s11999.0000000000000014
11. Tuca M, Bernal N, Luderowski E, Green DW. Tibial spine avulsion fractures: treatment update. Curr Opin Pediatr. 2019;31(1):103–111. doi:10.1097/MOP.0000000000000719
12. Bali K, Prabhakar S, Saini U, Dhillon MS. Open reduction and internal fixation of isolated PCL fossa avulsion fractures. Knee Surg Sports Traumatol Arthrosc. 2012;20(2):315–21. doi:10.1007/s00167-011-1618-6
13. Khatri K, Sharma V, Lakhotia D, Bhalla R, Farooque K. Posterior cruciate ligament tibial avulsion treated with open reduction and internal fixation through the burks and schaffer approach. Malays Orthop J. 2015;9(2):2–8. doi:10.5704/MOJ.1507.004.
14. Fan N, Zheng YC, Zang L, Yang CG, Yuan S, Du P, et al. What is the impact of knee morphology on posterior cruciate ligament avulsion fracture in men and women: a case control study. BMC Musculoskelet Disord. 2021;22(1):100. doi:10.1186/s12891–021-03984-5
15. Chen W, Luo W, Chen Z, Jiang Y. Treatment of posterior cruciate ligament avulsion fractures of the tibia using a toothed plate and hollow lag screw. Singapore Med J. 2016;57(1):39–44. doi:10.11622/smedj.2016010
16. Owesen C, Sandven-Thrane S, Lind M, Forssblad M, Granan LP, Årøen A. Epidemiology of surgically treated posterior cruciate ligament injuries in Scandinavia. Knee Surg Sports Traumatol Arthrosc. 2017;25(8):2384–91. doi:10.1007/s00167-015-3786-2
17. Sanders TL, Pareek A, Barrett IJ, et al. Incidence and long-term follow-up of isolated posterior cruciate ligament tears. Knee Surg Sports Traumatol Arthrosc. 2017;25(10):3017–23. doi:10.1007/s00167-016-4052-y
18. Joshi S, Bhatia C, Gondane A, Rai A, Singh S, Gupta S. Open reduction and internal fixation of isolated posterior cruciate ligament avulsion fractures: clinical and functional outcome. Knee Surg Relat Res. 2017;29(3):210–6. doi:10.5792/ksrr.17.022
19. Wu S, Zhang K, Fu W, Li J. Zhongguo xiu fu chong jian wai ke za zhi. 2023;37(5):572–7. doi:10.7507/1002-1892.202301061
20. Khalifa AA, Elsherif ME, Elsherif E, Refai O. Posterior cruciate ligament tibial insertion avulsion, management by open reduction and internal fixation using plate and screws through a direct posterior approach. Injury. 2021;52(3):594–601. doi:10.1016/j.injury.2020.09.058

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Original Article

Conservative Management of Pott's Spine and Its Outcome: An Institute-Based Observational Study

Rahil Jiwani, Sourabh Ghosh, Shubham Giri

Department of Orthopaedics, Bharati Vidyapeeth Medical College and Hospital, Sangli, India

Article History

Received: August 10, 2023
Accepted: October 23, 2023
Published: October 30, 2023

DOI: 10.15850/ijihs.v11n2.3512
IJIHS. 2023;11(2):92–98

Correspondence:
Sourabh Ghosh,
Department of Orthopaedics,
Bharati Vidyapeeth Medical College and Hospital– Sangli, India
Email: dr.sghosh007@gmail.com

Abstract

Objective: To analyze the functional outcome of cases with Pott's disease treated solely by antitubercular drugs.

Methods: This observational study was conducted at the Department of Orthopedics of a tertiary care medical college. Sixty patients with Pott's disease were included in this study based on predefined inclusion and exclusion criteria. All patients received antitubercular drugs for nine months. The Modified McCormick Scale (MSS) was used to assess the outcome of patients.

Results: Out of 60 patients, 37 (61.67%) were females, and 23 (38.33%) were males, with an M: F ratio of 1:0.62. Most patients had some or the other risk factors and belonged to low socioeconomic status. The most common presenting complaint was low back pain, and the thoracolumbar spine was most commonly involved. There was a significant improvement in the patient's functional status as assessed by the MSS score.

Conclusion: If diagnosed early, patients with Pott's disease can be treated solely by antitubercular treatment with excellent outcomes.

Keywords: Functional outcome, mccormick scale, pott's disease, tuberculous spondylitis

Introduction

Pott's disease is one of the forms of infection of the spine that is caused by *Mycobacterium tuberculosis.* This disease has been associated with significant morbidities and serious functional impairments, and comes second as the most common forms of tuberculosis after pulmonary tuberculosis.[1] In most cases, the initial symptoms are non-specific, requiring a high index of suspicion for an early diagnosis and prompt medical management. A delay in diagnosis and antitubercular treatment linked to catastrophic complications, such as paraparesis, scoliotic deformity, as well as paraplegia. This tubercular infection usually reaches the spine through a hematogenous route, and the common vertebral lesions include paradiscal, central, and anterior sub ligamentous lesions.[2] Symptoms in initial stages of Pott's disease are non-specific and, often times, they are attributed to less serious causes such as spondylosis. The common symptoms of Pott's disease include low grade fever, backache, unexplained weight loss, and local tenderness. A past history of pulmonary tuberculosis may be present in many cases. If untreated, neurological manifestations may occur, such as impaired sensations, radicular pain, paraparesis or paraplegia. Unlike in other spinal pathologies, the neurological complications due to Pott's disease are usually symmetrical and gradually progressive. In additon, the clinical presentation may differ depending upon the site of involvement, with thoracic spine as the most common site, followed by lumbar and cervical spine. If cervical spine is affected, complications such as stridor, dysphagia and, in serious cases, paraplegia or even quadriplegia may be observed.[3] Once suspected, the diagnosis of Pott's disease is usually confirmed through imaging techniques such as X-Ray, computed tomography (CT), and magnetic resonance

imaging (MRI). Though X-Ray of the spine is widely available, it has, however, a very low sensitivity for the diagnosis of Pott's disease, particularly in early stages, because in early stages of disease the vertebral space is usually preserved. In some cases, X-Ray may show reduced vertebral height with the irregularity of endplate. In untreated cases, the Pott's disease may present as gibbus deformity and vertebra plana. MRI is the imaging method of choice to assess the extent of involvement because it has a distinct advantage of showing the presence of epidural component of the involvement and cord compression. MRI may also show presence the paraspinal collection which may require a surgical intervention to be done.[4] The Pott's disease in majority of the cases managed by antitubercular drugs. Though the duration of treatment is a topic of debate majority of the researchers are of the opinion that the treatment should be continued for a total of 9 months. Total duration of treatment is divided into intensive phase (4 drugs given for 2 months) followed by continuation phase (2 drugs for 7 months). Surgical interventions are not needed if an early diagnosis is promptly followed by antitubercular treatment. In some cases, surgical procedures such as laminectomy, abscess drainage, costo-transversectomy, or anterolateral decompression may be required. Novel techniques, such as minimally invasive spine surgery and implantable devices, have also shown promising outcomes in selected cases.[5] This institution-based observational study was undertaken to analyze the functional outcome of cases with Pott's disease treated only by antitubercular drugs.

Methods

This was an observational study conducted at the Department of Orthopedics, Bharati Vidyapeeth Medical College and Hospital, Sangli, India. The study period was 2 years, starting from April 2021 to March 2023. During this period, 60 adult patients with Pott's disease treated solely by antitubercular drugs and having modified McCormick Scale (MSS) I, II or III at the time of presentation were included in this study. Patients having MSS IV or V at the time of presentation, as well as those with pre-existing neurological diseases likely to affect the functional outcomes and those with congenital or acquired spinal deformities were excluded from the study. The sample size was calculated on the basis of a pilot study done on patients with Pott's disease, by assuming 90% power and 95% confidence interval. Based on this calculation, the sample size required was 48 patients. By referring to the central limit theorem, sample size was determined to be adequate if it was more than 50. Thus, 60 patients were included. Demographic details, such as age, gender and socioeconomic status, were noted in all cases. A detailed history with respect to history of Kochs contact or any previous history of pulmonary or extrapulmonary tuberculosis was also collected and noted. Signs and symptoms including the presence of low-grade fever, backache or neurological symptoms, as well as the presence of sphincter involvement was also recorded and a thorough clinical examination was performed with respect to the presence of local tenderness or swelling over the affected part of spine. A thorough general and neurological exams were also performed. Deep tendon reflexes were elicited and the presence of any abnormality was noted. In all patients, routine investigations, such as complete blood count, erythrocyte sedimentation rate (ESR), and chest X-ray to rule out presence of active or previous pulmonary tuberculosis was conducted in all cases. Spine X-ray and magnetic resonance imaging was also performed in all cases. Percutaneous CT guided needle aspiration of abscess was done and the aspirate was sent for Acid fast bacillus (AFB) smear and culture sensitivity tests.

All patients received 2 months of intensive phase therapy using four drugs (isoniazid, 5 mg/kg; rifampicin, 15 mg/kg; ethambutol, 15–25 mg/kg; and pyrazinamide, 15–30 mg/kg) followed by continuation phase using two drugs (isoniazid and rifampicin) for 7 months. Patients were advised to do regular monthly follow up for 3 months and, after that, every 3 months for 15 months, with the last follow up visit scheduled 6 months after the completion of antitubercular treatment. In the follow up visits, routine investigations that included, among others, complete blood count, erythrocyte sedimentation rate (ESR), and detailed neurological examination were performed. The X-Ray of the affected spine was performed every 2 months. In selected cases, MRI was performed during follow up visits when the X-Ray showed an inconclusive result. At the time of final follow up visit, MRI was done in all the cases. Furthermore, during each follow up visit, the functional outcome was assessed using the MMS, which is used for assessment of global functional impairment in terms of neurological functions and walking

Table 1 Age Distribution and Socioeconomic Status

Demographic Profile		No of Cases	Percentage
Gender Distribution	Male	23	38.33%
	Female	37	61.67%
	Total	60	100 %
Age Group	18–30 years	7	11.67%
	31–40 years	21	35.00%
	41–50 years	17	28.33%
	Above 50 years	15	25.00%
	Total	60	100 %
	Mean Age	42.12 +/- 9.80 years	
Socio-Economic Status	Upper Class	1	1.67%
	Upper Middle Class	4	6.67%
	Middle class	15	25.00%
	Lower Middle Class	18	30.00%
	Lower Class	22	36.67%
	Total	60	100 %

ability[6]. The SPSS 21.0 software was used for data analysis and the descriptive statistics were depicted in the form of means and standard deviations for continuous variables, and frequencies, as well as percentages for the categorical variables. A p-value of less than 0.05 was considered as statistically significant.

Results

Sixty patients diagnosed with Pott's disease and treated by antitubercular drugs for 9 months were included in this study. Out of 60 patients, 37 (61.67%) were females and 23 (38.33%) were males with an M: F ratio of 1:0.62. The analysis of the age group of

Table 2 Predisposing Factors and Presented Complaints

Predisposing Factor and Presented Complaints		No of Patients	Percentage
Predisposing Factors	H/o Pulm Kochs	13	21.67%
	H/O Kochs Contact	7	11.67%
	Hypertension	3	5.00%
	Diabetes	5	8.33%
	Hypertension and DM	2	3.33%
	HIV infection	7	11.67%
	Steroids/Immunosuppressant	3	5.00%
Presented Complaints	Back pain	43	71.67%
	Low grade fever	34	56.67%
	Weight loss	23	38.33%
	Generalized weakness	13	21.67%
	Night sweats	5	8.33%
	Neurological manifestations	3	5.00%

Table 3 MRI Imaging Features and Affected Site in Studied Cases

	Age	No of cases	Percentage
MRI Imaging features	Vertebral body involvement	18	30.00%
	Disc Involvement	14	23.33%
	Endplate changes	12	20.00%
	Paravertebral Abscess	10	16.67%
	Gibbus deformity	6	10.00 %
	Total	60	100 %
Site of MRI changes	Thoracolumbar	32	53.33%
	Lumbar	16	26.67%
	thoracic	7	11.67%
	Lumbosacral	5	8.33%
	Total	60	100 %

the patients showed that the most common affected age group was between 31-40 years (35 %), which was followed by the 41-50 years (28.33 %) age group. The mean age of affected patients was found to be 42.12 +/- 9.80 years (Table 1). The distribution of the patients based on the Modified Kuppuswamy scale showed that the majority of the patients belonged either to lower class (36.67%) or lower middle class (30 %). Fifteen (25%) patients belonged to middle class and only 1(1.67%) patient belonged to upper class (Table 1).

The analysis of patients based on the predisposing factors or comorbidities showed that 13 (21.67%) patients had a history of previous antitubercular treatment. History of recent contact with Kochs patient was found in 7 (11.67%) patients, while 10 (16.67%) patients were having either diabetes mellitus or hypertension or a combination of both. Seven (11.67%) patients were HIV positive whereas 3 (5%) patients were on a long term steroid or immunosuppressant therapy. The analysis of patients on the basis of presented complaints showed that the most common presented complaint was low back pain, which was seen in 43 (71.67%) patients. The other common complaints included low grade fever (56.67%), weight loss (38.33%),

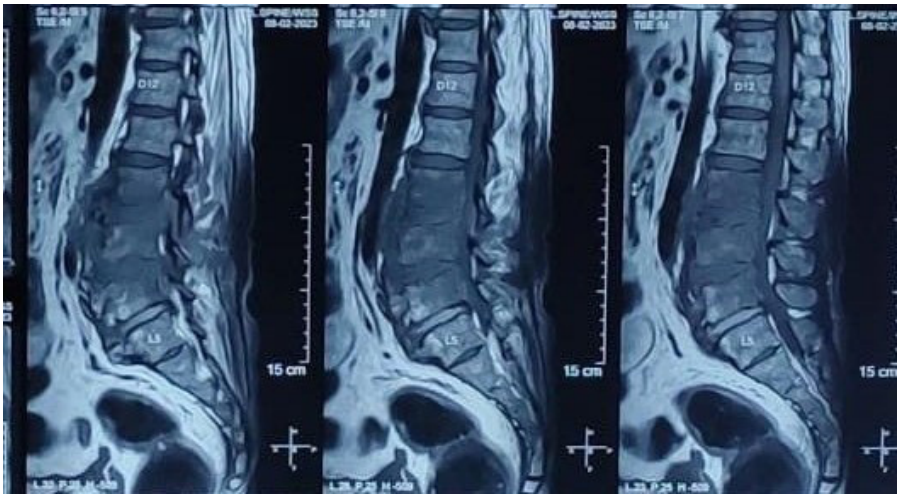

Fig. 1 Pre- and Para-Vertebral Collection Fusiform Observed as Extending From L2 to L4 of the vertebrae. Affected Vertebrae Appears Hypo Intense on T1. Features s/o Tuberculous spondylitis

Table 4 Modified McCormick's Scale (MMS) in Studied Cases During Follow Up

Modified McCormick's scale (MMS)	1st Consultation	3 months	6 months	9 months	12 months		15 months	
I	29 (48.33%)	35 (58.33%)	58 (96.67 %)	58 (96.67%)	59	98.33 %	59	98.33 %
II	25 (41.67%)	23 (38.33%)	2 (3.33%)	2 (3.33%)	1	3.33 %	1	3.33 %
III	6 (10%)	2 (3.33%)	0 (0.00%)	0 (0.00%)	0	0%	0	0%
IV	0	0 (0.00%)	0 (0.00%)	0 (0.00%)	0	0 %	0	0 %
V	0	0 (0.00%)	0 (0.00%)	0 (0.00%)	0	0%	0	0%
Mean MMS	1.61 +/- 0.66	1.46 +/- 0.56	1 .03 +/- 0.18	1 .03 +/- 0.18	1.01 +/- 0.12		1.01 +/- 0.12	

and weakness (21.67%). Night sweats and Neurological manifestations were reported by five (8.33%) and three (5.00%) patients, respectively (Table 2).

On clinical examination, point of maximal tenderness was found in the thoracolumbar region in 32 (53.33%) patients while lumbar, thoracic, and lumbosacral (8.33%) tenderness was observed in 16 (26.67%), 7 (11.67%) and 5 (8.33%) patients, respectively. All patients underwent MRI. The most common abnormality found on MRI was vertebral body involvement, which was seen as low signal on T1-weighted, high signal on T2-weighted images in 18 (30.00%) patients, followed by disc involvement in the form of loss of disc height and altered signal intensity seen in 14 (23.33%) patients. Endplate changes (20%), paravertebral abscess (16.66 %), and gibbus deformity (10%) were the other MRI findings (Table 3).

The functional assessment on the basis of MSS score showed that at the time of the first consultation, 29 (48.33%) patients belonged to the MSS I whereas 25 (41.67%) and 6 (10%) patients belonged to scale II and III, respectively. At the time of the final follow up at 15 months, 59 (98.33%) patients were found to have am MSS score of I with intact neurologically and no sensory or motor abnormalities and one (1.67%) patient had an MSS score of II with mild sensory deficit but functionally independent. There was remarkable improvement in functional status of the patient as assessed by the MSS score and the difference was highly significant statistically ($p<0.0001$) (Table 4).

Discussion

In this study, patients with Pott's disease and treated solely by antitubercular management were studied. Out of 60 patients, 37 (61.67%) were females and 23 (38.33%) were males with an M:F ratio of 1:0.62. Jagiasi *et al.*[7] in their study of 44 patients diagnosed as Tuberculous spondylitis to delineate the importance of middle path regime and short course chemotherapy in the management of spine tuberculosis[7] also showed a significant male preponderance, with 10 (22.73%) males and 34 (77.27%) females. Similar female preponderance was also reported by other authors, such as Kothari[8] and Peer *et al.*[9]

The mean age of patients in this study was found to be 42.12+/-9.80 years. Wang *et al.*[15] collected data from 597 patients with Pott's disease with no major neurological deficits or severe spinal deformities. Their study population consisted of 313 males (52.43 %) and 284 females (47.57 %) with a mean age of 43 years (range 13–89 years), which is similar to the mean age of this present study. Similar mean age of patients with Pott's spine was also reported by the authors, such as Divya *et al.*[11] and Mittal *et al.*[12]. The analysis of patients on the basis of predisposing factors or presence of co-morbidities showed that 13 (21.67%) patients had history of having received antitubercular treatment in past. History of recent contact with Kochs patient was found in seven (11.67%) patients. Other predisposing factors in this study were immunosuppression due to HIV and long-term steroid therapy. Previous history of pulmonary tuberculosis and immunocompromised status were the common factors leading to Pott's disease stated in many the studies. Vaishnav B *et al.* in an observational study of 100 cases of Pott's spine[13] also showed that the majority of the patients had a previous history of pulmonary tuberculosis. Similar predisposing factors were also reported by other authors, such as Jurcev-Savicevic *et al.*[14] In this study,

the majority of patient's belonged to the lower and lower middle classes, and poor socioeconomic status was a significant factor associated with patients suffering from Pott's disease. Glassman *et al.*[15] have also reported malnutrition and poverty as one of the significant risk factors for developing Pott's disease.

The most common area involved in this present study was the thoracolumbar area. MRI showed involvement of either thoracic or lumbar or thoracolumbar vertebrae in the majority of the cases (91.67%). Only five (8.33%) patients showed an involvement of the lumbosacral area. The most common abnormality found on MRI was vertebral body involvement, which was seen as low signal on T1-weighted, high signal on T2-weighted images (30.00%), followed by disc involvement (23.33%), endplate changes (20%), paravertebral abscess (16.66 %), and gibbus deformity (10%). Misra *et al.*[16] studied the MRI findings in 36 patients with Pott's disease, and vertebral changes in form of spondylodiscitis in 33 (92%) patients, epidural abscess in 29 (81%) patients, spinal cord changes including edema and granuloma in 17 (47%) patients, paravertebral abscess in 29 (81%) patients, and vertebral body collapse in 12 (33.3%) patients. were reported. Similar MRI findings in cases of Pott's disease was also reported by other authors such as Rivas-Garcia *et al.*[17] and Kubihal *et al.*[18]

In terms of treatment, there was a significant improvement in functional status of the patient as assessed by the MSS score and the difference was highly significant statistically ($p<0.0001$). No patient had been affected significantly in terms of functional independence, and only one patient experienced mild sensory disturbance at the time of final follow up. This excellent outcome after complete course of antitubercular treatment was also reported by other authors, such as Talebzadeh *et al.*[19] and Bakhsh *et al*.[20]

Patietns with Pott's disease or tubercular spondylitis needs early diagnosis and prompt antitubercular treatment, which is provided in an adequate period of time. Patients who are diagnosed early can be successfully treated by antitubercular drugs without any need for surgical interventions. The majority of the adequately treated patients have excellent functional outcomes without any residual motor or sensory disturbance.

The main limitation of this study was that it is a purely observational study. More randomized controlled trials are needed to further substantiate the findings of this study.

In conclusion, patients with Pott's disease can be treated solely by antitubercular treatment and have excellent outcomes and remain intact neurologically with no sensory or motor abnormalities when diagnosed early.

References

1. Rajasekaran S, Soundararajan DCR, Shetty AP, Kanna RM. Spinal tuberculosis: current concepts. global spine J. 2018; 8(4 Suppl):96S–108S. doi:10.1177/2192568218769053
2. Ansari S, Amanullah MF, Ahmad K, Rauniyar RK. Pott's Spine: diagnostic imaging modalities and technology advancements. N Am J Med Sci. 2013;5(7):404–11. doi:10.4103/1947-2714.115775
3. Ayele BA, Wako A, Tadesse J, Gulelat H, Ibrahim R, Molla S, et al. Pott's paraplegia and role of neuroimaging in resource limited setting: A case report and brief review of the literatures. J Clin Tuberc Other Mycobact Dis. 2021;25:100283. doi:10.1016/j.jctube.2021.100283.
4. Misra UK, Warrier S, Kalita J, Kumar S. MRI findings in pott's spine and correlating clinical progress with radiological findings. Neuroradiol. 2020;62(7):825–32. doi: 10.1007/s00234-020-02402-2
5. Patel PD, Canseco JA, Houlihan N, Gabay A, Grasso G, Vaccaro AR. Overview of minimally invasive spine surgery. World Neurosurg. 2020;142:43-56. doi:10.1016/j.wneu.2020.06.043
6. Rajasekaran S, Soundararajan DCR, Shetty AP, Kanna RM. Spinal tuberculosis: current concepts. global spine J. 2018; 8(4 Suppl):96S–108S. doi:10.1177/2192568218769053
7. Ansari S, Amanullah MF, Ahmad K, Rauniyar RK. Pott's spine: diagnostic imaging modalities and technology advancements. N Am J Med Sci. 2013; 5(7):404–11. doi:10.4103/1947-2714.115775
8. Ayele BA, Wako A, Tadesse J, Gulelat H, Ibrahim R, Molla S, et al. Pott's paraplegia and role of neuroimaging in resource limited setting: a case report and brief review of the literatures. J Clin Tuberc Other Mycobact Dis. 2021;25:100283.

doi:10.1016/j.jctube.2021.100283.
9. Misra UK, Warrier S, Kalita J, Kumar S. MRI findings in Pott's spine and correlating clinical progress with radiological findings. Neuroradiology. 2020; 62(7):825–32. doi:10.1007/s00234-020-02402-2
10. Patel PD, Canseco JA, Houlihan N, Gabay A, Grasso G, Vaccaro AR. Overview of minimally invasive spine surgery. World Neurosurg. 2020; 142:43–56. doi:10.1016/j.wneu.2020.06.043
11. Bellut D, Burkhardt JK, Mannion AF, Porchet F. Assessment of outcome in patients undergoing surgery for intradural spinal tumor using the multidimensional patient-rated Core Outcome Measures Index and the modified McCormick Scale. Neurosurg Focus. 2015;39(2):E2. doi:10.3171/2015.5.FOCUS15163
12. Jagiasi JD, Patel MR. Results of management of spinal tuberculosis according to middle path regime and short course chemotherapy. Int J Res Orthop. 2017;3:966–72. http://dx.doi.org/10.18203/issn.2455-4510.IntJResOrthop20173672
13. Kothari MK, Shah KC, Tikoo A, Nene AM. Surgical management in elderly patients with tuberculous spondylodiscitis: ten year mortality audit study. Asian Spine J. 2016;10(5):915–9. doi:10.4184/asj.2016.10.5.915.
14. Peer V, Schwartz N, Green MS. Gender differences in tuberculosis incidence rates-A pooled analysis of data from seven high-income countries by age group and time period. Front Public Health. 2023;10:997025. doi: 10.3389/fpubh.2022.997025.
15. Wang P, Liao W, Cao G, Jiang Y, Rao J, Yang Y. Characteristics and management of spinal tuberculosis in tuberculosis endemic area of Guizhou Province: a retrospective study of 597 patients in a Teaching Hospital. Biomed Res Int. 2020;2020:1468457. doi:10.1155/2020/1468457
16. Divya A, Shukla DP, Bahubali VH, Bharath RD, Nandeesh BN, Kruthika P, et al. Consumption of spine by tuberculosis in the era of directly observed treatment, short-course and genomic diagnosis. Indian J Tuberc. 2021;68(1):73–9. doi:10.1016/j.ijtb.2020.08.017.
17. Mittal S, Yadav G, Ahuja K, Ifthekar S, Sarkar B, Kandwal P. Predicting neurological deficit in patients with spinal tuberculosis-A single-center retrospective case-control study. SICOT J. 2021;7:7. doi:10.1051/sicotj/2021002.
18. Vaishnav B, Suthar N, Shaikh S, Tambile R. Clinical study of spinal tuberculosis presenting with neuro-deficits in Western India. Indian J Tuberc. 2019;66(1):81–6. doi:10.1016/j.ijtb.2018.04.009
19. Jurcev-Savicevic A, Mulic R, Ban B, et al. Risk factors for pulmonary tuberculosis in Croatia: a matched case-control study. BMC Public Health. 2013;13:991. doi:10.1186/1471-2458-13-991
20. Glassman I, Nguyen KH, Giess J, Alcantara C, Booth M, Venketaraman V. Pathogenesis, diagnostic challenges, and risk factors of pott's disease. Clin Pract. 2023;13(1):155–65. doi:10.3390/clinpract13010014.
21. Misra UK, Warrier S, Kalita J, Kumar S. MRI findings in Pott's spine and correlating clinical progress with radiological findings. Neuroradiology. 2020;62(7):825–32. doi:10.1007/s00234-020-02402-2.
22. Rivas-Garcia A, Sarria-Estrada S, Torrents-Odin C, Casas-Gomila L, Franquet E. Imaging findings of Pott's disease. Eur Spine J. 2013;22 Suppl 4(Suppl 4):567–78. doi:10.1007/s00586-012-2333-9
23. Kubihal V, Sharma R, Krishna Kumar RG, Chandrashekhara SH, Garg R. Imaging update in spinal tuberculosis. J Clin Orthop Trauma. 2021; 25:101742. doi:10.1016/j.jcot.2021.101742
24. Talebzadeh AT, Talebzadeh N. Diagnosis, management, and prognosis of spinal tuberculosis: a case report. Cureus. 2023;15(2):e35262. doi:10.7759/cureus.35262
25. Kumar K. Spinal tuberculosis, natural history of disease, classifications and principles of management with historical perspective. Eur J Orthop Surg Traumatol. 2016;26(6):551–58. doi:10.1007/s00590-016-1811-x

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Original Article

Association between Comorbidities and COVID-19 Mortality: a Cross-Sectional Study in a Community Health Center in Indonesia

Sutaip, Dwi Sutiningsih, Mateus Sakundarno Adi, Sutra Diyana, Siti Rahayu, Nur Azizah Azzahra, Puti Andalusia Sarigando Banilai, Giyantolin

Master of Epidemiology, Postgraduate School, Diponegoro University, Semarang, Indonesia

Article History

Received: February 04, 2023
Accepted: October 17, 2023
Published: October 30, 2023

DOI: 10.15850/ijihs.v11n2.3216
IJIHS. 2023;11(2):99–106

Correspondence:
Dwi Sutiningsih, Master of Epidemiology, Postgraduate School, Diponegoro University, Semarang, Central Java, Indonesia
Email: dwi.sutiningsih@live.undip.ac.id

Abstract

Objective: To analyze the risk factors for mortality and comorbidity of COVID-19 patients in a public health center work area in Indonesia.

Methods: This was a cross-sectional observational analytic quantitative study using secondary data of 820 confirmed COVID-19 cases in Brebes Public Health Center work area during the period of June 2020–December 2021. Univariate and bivariate analyses were used to analyze the obtained data statistically with a p-value of <0.005 considered significant.

Results: Of the 820 confirmed COVID-19 patients, 85.1% recovered and 15.0% died. Analysis on the characteristics of these cases showed that 51.2% females and 48.8 % males were included in this study, with 77.6% of them were <60 years old. No history of comorbidities was identified in 92.1% of the cases. In remaining cases with comorbidities, Diabetes Mellitus was recognized as the most prevalent (n=39, 4.8%). Results of the Chi-Square test demonstrated that comorbidity status (p-value= 0.001), place of quarantine (p=0.000; p>0.05), and diabetes (p=0.000, OR =2.87, 95% CI 19 1.24–0280) were significantly associated with mortality.

Conclusion: Comorbidity status, diabetes, and the place quarantine are risk factors for mortality among COVID-19 confirmed cases, especially in Brebes Public Health Center work area. Thus, it is important to increase knowledge about COVID-19 prevention and risks to prevent transmission among those with higher risks for mortality. Further studies on factors related to sustainable supports for COVID-19 patients are also necessary.

Keywords: Characteristics, comorbidity, COVID-19, risk factors

Introduction

During the pandemic, the number of COVID-19 cases continued to increase, progressed very quickly, and spread globally. COVID-19 is a disease caused by the Severe Acute Respiratory Syndrome Coronavirus *2* (SARS-CoV-2) that is transmitted from human to human, with a potential aerosol transmission. Transmission becomes easier on a closed environment as this kind of environment can support a high concentration of virus that persist for a longer time.[1] With its highly transmissible characteristics, the virus had been able to maintain the COVID-19 pandemic for year and the number of cases continued to increase daily.[1] As of December 15, 2021, the WHO reported 318,648,834 confirmed cases with 518,343 deaths worldwide (CFR 1.7%). In the same period, Indonesia recorded 4,270,794 confirmed cases, 4,118,164 recovered cases (96.4%), 7,877 active cases (0.2%), and 144,167 deaths(CFR 3.4%).[2] The province with the highest number of cases was DKI Jakarta with COVID-19 positive patients of 870,363, 852,973 recovered, and 13,611 died. The second rank was occupied by West Java Province with 709,515 cases, 693,895 recovered, and 14,761 died, followed by Central Java in the third rank with 487,098 cases, 455,763 recovered (RR 93.56%), and 30,297 died (CFR 6.2%). Despite the fact that

Central Java ranked third in the daily cases as of December 15, 2021, it ranked first in terms of the cumulative deaths due to COVID-19.[3] In Brebes district, as of December 15, 2021, 14, 177 cases were confirmed, 12,405 recovered completely, and 1,607 died (CFR 8.8%). In the sampe period, in five community centers in Brebes District, it was recorded that in Brebes Community Health Center (Puskesmas), 1,775 confirmed cases was registered with 244 deaths. Meanwhile, in Puskesmas Buniayu, 1,587 confirmed cases were recorded with 127 deaths. In Puskesmas Banjarharjo and Puskesmas Bulakamba, 1,095 and 1,108 cases were confirmed with 100 and 177 deaths, respectively. In addition, Puskesmas Ketanggungan recorded 850 confirmed cases and 99 deaths.[4] Current studies on this disease have identified several groups as the most vulnerable group for COVID-19 including the elderly, health workers, smokers, vape users, men, and individuals with blood type A. Furthermore, SARS CoV-2 is also more easily transmitted to those who are immunocompromised and those with commorbidities.[5]

The signs and symptoms of COVID-19 are generally similar to other respiratory infections, such as fever, cough, and shortness of breath. In severe cases, COVID-19 could cause pneumonia, respiratory failure, kidney disease, and even death.[6,7] Based on a study by Dessie *et al*., several risk factors influence the risk for mortality due to coronavirus, such as chronic comorbidities, complications, acute kidney injury, chronic obstructive pulmonary disease, hypertension, cardiovascular diseases (CVD), cancer, increased D-dimer level, male gender, older age, active smoking, and obesity.[8] In a previous study, Djaharuddin *et al*.[9] stated that most deaths linked to comorbidities occured in patients with hypertension, cardiovascular disease, and diabetes. These authors also stated that more than half of the patients (52.56%) who died due to COVID-19 had ≥2 comorbidities, with the remaining had one comorbidity.[9] This study aimed to analyze the relationship between risk factors for case fatality and comorbidities in COVID-19 cases in Brebes District, Central Java, Indonesia.

Methods

This was a quantitative study using a cross-sectional observational analytic approach on data collected from Puskesmas Brebes during the period June 2020–December 2021. A total of 820 cases was included and demographic data such as patient status, age, gender, comorbidities, treatment history, and symptoms were collected. Data were obtained from the patient medical record of confirmed COVID-19 patients of Puskesmas Brebes. The inclusion criteria were patients diagnosed with COVID-19 at Puskesmas Brebes during the period of June 2020 - December 2021, while the exclusion criterion was incomplete medical records. The scoring criteria used were: recovered (1) and died (2) for age; male (1) and female (2) for gender; >60 years (elderly) (1) 45–59 years (pre-elderly); and 19–44 years (adult) (2); 10–18 years (adolescent); 6–9 years (Child) (3), 1–5 years (under-five) (4), and 0 years (infant) (5) for age. In addition, a yes/no scoring was applied for comorbidities with Yes being 1 and No being 2. The comorbidities analyzed in this study were diabetes mellitus, hypertension, pneumonia/acute respiratory infection (ARI), cardiovascular disease, rheumatoid arthritis, and asthma. All data were then tested statistically using the Chi-square test. Microsoft Excel and SPSS v.24 were used to perform univariate and bivariate (Chi-square test) analyses.

Results

The characteristics of COVID-19 patients in this study were listed in Table 1. Of the 820 confirmed COVID-19 cases, 85.1% were

Table 1 Characteristic Distribution of Cases (n=820)

Variable	n=820	%
Patient Status		
Recovered	698	85.0
Died	122	15.0
Gender		
Male	400	48.8
Female	420	51.2
Age		
>60 years (Elderly)	183	22.5
45–59 years (Pre-elderly)	261	31.8
19–44 years (Adult)	321	39.3
10–18 years (Adolescent)	25	3.1
6–9 years (Child)	11	1.3
1–5 years (Under-Five)	14	1.7
0 years (Infant)	5	6

declared recovered, while 15.0% ended in fatality. The number of male and female cases was almost similar (51.2% vs. 48.8 %). The majority of cases was found in the <60 years old group (77.6%).

Table 2 presents that 92.1% of the patients in this study did not have any comorbidity, leaving only 7.9% of them suffered from comorbidities. The most prevalant comorbidity was diabetes mellitus, which was recognized in 39 patients (4.8%).

The history of hospitalization is presented in Table 3. Approximately two third of the patients (n=548, 66.8 %) had a history of hospitalization and the remaining one third underwent self-isolation (n=272, 33.2 %). Most patients referred for hospitalization were treated at Brebes District General Hospital (n=299, 36.5%).

Statistically, the relationship between variables in this study was considered to be significant if the p-value was less than <0.05. The results of the Chi-square test on the relationship between COVID-19 confirmed case and studied variables showed that confirmed COVID-19 cases was significantly associated with comorbidity status (p-value=0.001, OR 0.383, 95% CI (19) 0.216–0.680), meaning that patients with comorbidity had a risk probability that was 0.383 times higher to be declared as confirmed COVID-19 cases (Table 4); Diabetes (p-value=0.000, OR 2.87, 95% CI 19 1.24-0280) showing that patients with a history of diabetes had a 2.87 times higher risk to die due to COVID-19 (Table 4); and the place of quarantine (p-value =0.000. In addition, place of quarantine was also found to be

Table 2 Characteristic Distribution Patient Confirmed COVID-19 based on Comorbidities

Variable	n=820	%
Comorbidity Status		
Yes	65	7.9
No	755	92.1
Diabetes Mellitus (DM)		
Yes	39	4.8
No	781	95.2
Hypertension		
Yes	20	2.4
No	800	97.6
Pneumonia/ARI		
Yes	9	1.1
No	811	98.9
Heart Failure		
Yes	3	0.4
No	817	99.6
Rheumatoid Arthritis		
Yes	1	0.1
No	819	99.9
Asthma		
Yes	1	0.1
No	819	99.9

Table 3 Distribution of COVID-19 Confirmed Case by Place of Quarantine

Place of Quarantine	n=820	%
Self-Isolation at Home or Puskesmas	272	33.2
Hospitalized	548	66.8
Dr. Kariadi National General Hospital	6	0.7
Brebes District General Hospital	299	36.5
Bhakti Asih General Hospital	109	13.3
Harapan Anda Islamic General Hospital	58	7.1
Mitra Keluarga General Hospital	17	2.1
Hermina Panandaran General Hospital	2	0.2
Kardinah City General Hospital Tegal	20	2.4
Dr. Soeselo District General Hospital Tegal	11	1.3
Mutiara Bunda Islamic General Hospital	3	0.4
Mitra Siaga Tegal Hospital	4	0.5
RS Bhakti Asih Kec. Jatibarang	6	0.7
RSUD Dedy Jaya Brebes	11	1.3
RSUD Surodadi Tegal	1	0.1
RS Harapan Sehat Bumiayu	1	0.1

Table 4 Correlation Between Death and Comorbidities

Variable	Status				p	OR	95% CI	
	Recovered		Died				Lower	Upper
	n	%	n	%				
Comorbidity						0.383	0.216	0.679
Yes	46	6.6	19	15.7	0.001			
No	652	93.4	103	84.3				
Diabetes						2.87	0.144	0.569
Yes	25	3.6	14	11.5	0. 000			
No	673	96.4	108	88.5				
Hypertension						0.514	0.183	1.441
Yes	15	2.1	5	4.1	0.198			
No	683	97.9	117	95.9				
ARI						0.608	0.125	2.961
Yes	7	1	2	1.6	0.534			
No	691	99	120	98.4				
Heart Failure						1.176	1.142	1.210
Yes	3	0.4	0	0	0.468			
No	695	99.6	122	100				
RD Arthritis						1.175	1.142	1.209
Yes	1	0.1	0	0	0.676			
No	697	99.9	122	100				
Asthma						1.175	1.142	1.209
Yes	1	0.1	0	0	0.676			
No	697	99.9	122	100				

significantly linked to the death of confirmed COVID-19 cases with (p-value=0.000) (Table 5).

Discussion

The presence of comorbidities was shown to be linked to mortality in this present study. This result supports the finding of a study in Ternate City, North Maluku, which reported that comorbidities like hypertension, diabetes mellitus type 2, and asthma have a significant relationship (p-value≤0.05) with the severity of COVID-19 disease.[6] The same finding is also presented by a meta-analysis study showing that the existence of comorbidities

Table 5 Relationship Between Place of Quarantine and Mortality in COVID-19

Variable	Status				p	95% CI		
	Recovered		Died			OR	Lower	Upper
	n	%	n	%				
Place of Quarantine and Treatment						0.777	0.743	0.813
Hospital	426	61	122	100	0.00			
Self-isolation	272	39	0	0				

in COVID-19 patients increases the severity of the disease approximately three times higher (OR=2.85, 95% CI 2.09-3.89).[7] This is caused by the changes in the pathophysiology-related mechanism where chronic comorbidity causes dysregulation of the main physiological systems, including hypothalamus-pituitary-adrenal axis, sympathetic nervous system, and immune system.[8] COVID-19 virus can also induce or worsen the condition by binding to the Angiotensin-Converting Enzyme 2 (ACE2) receptors, which are widely distributed in various organs. This will lead to disturbances in the organ, such as causing the dysregulation of the renin-angiotensin-aldosterone system (RAAS) that leads to hemostatic, nervous, and main physiological system disturbances, making the patient more prone to organ failure that will eventually increase COVID-19 complications and eventually result in mortality.[9] This study found that the type of comorbidity also influence the the relationship betwee comorbidity and confirmed case, with diabetes mellitus having a significant relationship with confirmed COVID-19 cases (p-value=0.000). This is similar to the results of a previous study by Lee *et al.* that diabetes mellitus type 2 can increase the severity of COVID-19 patients by 1.55 times when compared to COVID-19 patients without DM.[10] COVID-19 patients with diabetes mellitus will have increased secretion of hyperglycemic hormones such as catecholamines and glucocorticoids, leading to elevated blood glucose variability, abnormal glucose level, and diabetes complications.[11] Diabetes is one of the main risk factors for COVID-19. This may be due to the fact that diabetic people are more susceptible to infection because of their hyperglycemia status, immune function disorders, vascular diseases such as hypertension, dyslipidemia, and cardiovascular disease. The disease severity and mortality of COVID-19 patients are higher in diabetic patients compared to non-diabetic patients.[12]

People suffering from diabetes mellitus with COVID-19 are observed to have increased secretions of hyperglycemic hormones, such as catecholamines and glucocorticoids, that will, in turn, produce elevated blood glucose, abnormal glucose variability, and diabetes complications.[12] Two previous studies in Indonesia also found a similar result where diabetes mellitus is identified as a comorbidity that can increase the severity of COVID-19 by 3.4 times and increase the risk for mortality 4.4 times compared to non-diabetic patients.[13,10]

In contrast, hypertension was not proven to have a significant relationship with the incidence of COVID-19 (p-value=0.119). This supports the finding of a study in 2020 that also used Chi-square test that hypertension is found to have no significant relationship with confirmed COVID-19 case (p-value=0.414) .[17]

Contrary those findings, Li *et al.*[18] found that 17.1% of patients with a history of infectious diseases experience comorbidities, including hypertension after they studied 1,527 patients treated in ICU and non-ICU. Therefore, hypertension is considered to be a comorbid of COVID-19. Several other studies also show that the presence of hypertension as a comorbid could worsen the prognosis of COVID-19 caused by the consumption of ACE inhibitors and ARBs as hypertension drugs, which could exacerbate COVID-19.[18] Theoretically, the underlying mechanism of the link betwen hypertension and COVID-19 is still unknown. However, considering the important role of RAS (Renin Angiotensin System)/ACE-2 in the pathophysiology of hypertension, a dysregulation of the system may be the important link for this mechanism. A suggestion has also been given regarding the possiblity that hypertension therapy using the SRA inhibitors can affect the binding process of SARS-CoV-2 to ACE-2 to support the infection process. Suggestions based on experimental findings also stated that RAS inhibitors that cause ACE-2 expression enhancement as compensation for ACE blockers can be detrimental in patients exposed to SARS-CoV-2.[19]

There is also no significant relationship found between ARI and confirmed COVID-19 cases in this study (p=0.535), which is in line with a study by Komang that demonstrated no connection between ARI and the incidence of COVID-19 (p>0.05).[20] Another study performed on community health center in 2020 also confirmed that based on the bivariate analysis, pneumonia is not significantly correlated with the incidence of COVID-19.[6]

In severe cases, COVID-19 can exacerbate into acute respiratory distress syndrome, sepsis, septic shock, as well as multi-organ failures, including kidney or heart failure.[21] No significant relationship was found between heart failure and confirmed COVID-19 cases (p-value=0.468). This finding is in line with a similar study by Steven *et al.*, which presented no significant relationship between history of hearth disease and vulnerability for COVID-19 (p-value =0.828).[19] In contrast, Zheng et al. in their study found that patients with

cardiovascular hypertension and coronary heart disease (CHD) have a higher risk of experiencing more severe manifestations when infected by SARS-CoV-2, which then contribute to a significant part of mortality caused by COVID-19. This is probably because of the higher ACE2 expression in patients with cardiovascular disease.[18] Patients who are >60 years old infected by SARS-CoV-2 can experience more systemic and critical pneumonia manifestations when compared to younger patients, and their condition may be aggravated by cardiovascular disease.[22] Patients with a history of cardiovascular disease could become unstable during the course of SARS-CoV-2. Patients with Acute Coronary Infection Syndrome (ACS) who are infected with SARS-CoV-2 often have a poor prognosis. In these patients, the reduced heart function will lead to ischemia or mycardial necrosis which will stop the heart. Some COVID-19 patients in Wuhan who had a history of ACS experienced a more severe disease and the mortality rate for this group of patients is higher.[20, 21] The difference between the result of this study in terms of cardiovascular disease as a comorbid of COVID-19 may stem from the fact that only a a small number of subjects in the sample that take ACEIs or ARBs routinely.

Asthma is also shown as having no significant relationship with confirmed COVID-19 cases (p=0.676 >0.05). Coronavirus is a virus that attacks the respiratory system and produces similar symptoms as other respiratory viruses. Respiratory viruses may lead to asthma symptoms that can be life-threatening. The World Health Organization also lists tasthma, diabetes, and heart diseases as conditions that make an individual more susceptible to coronavirus infection. Coronavirus attacks the lungs, and then damages the heart. Individuals with cardiovascular disease and hypertension have a higher risk of getting infected and experiencing fatality due to coronavirus infection. The infection caused by the coronavirus seems to be more critical than other viruses because it can cause damages to the heart muscle and trigger heart injuries like pericarditis and myocarditis.

According to a study by Winogroho *et al*.,[23] the place of quarantine has a significant influence on the healing process and shortens the exposure period to COVID-19 among nurses. This study showed that the place quarantine contributes positively to the length of quarantine time. Individual will feel more comfortable if they are quarantined in a comfortable and supportive environment for the healing process. This is in line with a study by Wang *et al*. that stated nosocomial infection is hazardous for the patient, other patients, and healthy people.[24] Zhongnan Hospital reported a case where a patient was admitted due to stomach ache to the same hospital for COVID-19 patients and eventually suffered from COVID-19. Furthermore, more than ten hospital workers were infected with this disease in the same hospital. This is in line with the risk factors stated by the US Centers for Disease Control and Prevention (CDC) that include close contact, living in the same house with a COVID-19 patient, and a history of traveling to areas affected by COVID-19. The risk is considered low when there is no close contact (in a radius of 2 meters).[25] Currently, SARS-CoV-2 is transmitted from human to human, leading to aggressive transmission of the disease. This virus is transmitted from symptomatic patients through droplets that are propelled during coughing or sneezing. [22,26] The virus can also be transmitted through aerosols that could penetrate the body, especially the lungs, through inhalation through the nose or mouth. The coronavirus also shows a higher level of transmission than SARS due to the genetic recombination that increases transmission ability.[27]

In this study, only COVID-19 cases recorded at the Brebes Community Health Center were analyzed. For this reason, further comprehensive studies are needed to determine the risk factors that influence COVID-19 comorbidity and mortality.

In conclusion, the risk factors that are significantly associated to confirmed COVID-19 cases and deaths in the work area of Brebes Community Health Center are comorbidity status, especially diabetes, and the place of quarantine, with diabetes mellitus as the factor that is linked to the highest mortality. It is suggested that community should increase their knowledge on COVID-19 prevention and that follow up studies are needed for this isssue.

Acknowledgements

This publication was funded by the SEAOHUN Scholarship Program under the support of the United States Agency for International Development (USAID) One Health Workforce -Next Generation (OHW-NG) Award 7200AA19CA00018.

References

1. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102–8. doi:10.1016/j.jpha.2020.03.001
2. WHO. WHO COVID-19 Dashboard [Internet]. World Health Organization. 2022. Available from: https://covid19.who.int/
3. BBC. Coronavirus confirmed as pandemic by World Health Organization - BBC News. 2020.
4. Brebes District Health Office. COVID-19 Case Data. Brebes: Brebes District Health Office; 2022.
5. Destylya D. Karakteristik Pasien Covid-19 Di Rumah SakitUmum Pusat Haji Adam Malik MedanSumatera Utara. 2021;
6. COVID-19 incidence and mortality in non-dialysis chronic kidney disease patints., et al. COVID-19 incidence and mortality in non-dialysis chronic kidney disease patints. PLoS One. 2021;16(7):e0254525. Published 2021 Jul 9. doi:10.1371/journal.pone.0254525
7. Johnson KD, Harris C, Cain JK, Hummer C, Goyal H, Perisetti A. Pulmonary and extra-pulmonary clinical manifestations of COVID-19. Front Med (Lausanne). 2020;7:526. doi:10.3389/fmed.2020.00526
8. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. BMC Infect Dis. 2021;21(1). doi:10.1186/s12879-021-06536-3
9. Djaharuddin I, Munawwarah S, Nurulita A, Ilyas M, Ahmad N. Comorbidities and mortality in COVID-19 patients. Gac Sanit. 2021;35(S2):S530–2. doi:10.1016/j.gaceta.2021.10.085
10. Ndera ML, Supriyatni N, Rahayu A. Faktor komorbid terhadap covid-19 di Puskesmas Kota Tahun 2020. J BIOSAINSTEK. 2021;3(2):1–9. doi: https://doi.org/10.52046/biosainstek.v3i2.723
11. Radwan NM, Mahmoud NE, Alfaifi AH, Alabdulkareem KI. Comorbidities and severity of coronavirus disease 2019 patients. Saudi Med J. 2020;41(11):1165–74. doi:10.15537/smj.2020.11.25454
12. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. PLoS One. 2020;15(8):e0238215. doi:10.1371/journal.pone.0238215
13. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020;17(9):543-558. doi:10.1038/s41569-020-0413-9
14. N Lestari, I Burhannudin. Diabetes melitus sebagai faktor risiko keparahan dan kematian pasien covid-19: meta-analisis. Biomedika. 2021;13(1):83–94. doi: 10.23917/biomedika.v13i1.13544
15. Galvão Tessaro FH, Ayala TS, Bella LM, Martins JO. Macrophages from a type 1 diabetes mouse model present dysregulated Pl3K/AKT, ERK 1/2 and SAPK/JNK levels. Immunobiology. 2020;225(2):151879. doi:10.1016/j.imbio.2019.11.014
16. Sugawara E, Nikaido H. Properties of AdeABC and AdeIJK efflux systems of Acinetobacter baumannii compared with those of the AcrAB-TolC system of Escherichia coli. Antimicrob Agents Chemother. 2014;58(12):7250–7. doi:10.1128/AAC.03728-14
17. Rifiana AJ, Suharyanto T. Hubungan diabetes mellitus dan hipertensi dengan kejadian corona virus deases-19 (Covid-19) di Wisma Atlit Jakarta Tahun 2020. Univ Nas. 2020;19:1–15.
18. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109(5):531–8. doi:10.1007/s00392-020-01626-9
19. Firdaus I, Sukmawan R, Anwar Santoso DAJ, Firman D, Akbar N. Panduan diagnosis dan tatalaksana penyakit kardiovaskular pada pandemi covid-19. In: Perhimpunan Dokter Spesialis Kardiovaskular Indonesia. 2020.
20. Kisid K, Putri EBA. Kejadian Covid-19 berdasarkan karakteristik pengunjung Poli ISPA Puskesmas Perampuan Lombok Barat. J Penelit dan Kaji Ilm. 2021;7(2):169–75. doi: https://doi.org/10.33651/jpkik.v7i2.276
21. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–81. doi:10.1016/S2213-2600(20)30079-5
22. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol.

2020;17(5):259–60. doi:10.1038/s41569-020-0360-5
23. Winugroho T, Imansyah M, Bangun E, Apriyadi RK, Hidayat A. Analisis pengaruh faktor demografi terhadap lama karantina pada perawat terpapar Covid-19 di Jawa Tengah. PENDIPA J Sci Educ. 2021;5(2):229–36. https://doi.org/10.33369/pendipa.5.2.229-236
24. Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care. 2020;24(1):1–9. doi:10.1186/s13054-020-02895-6
25. Centers for Disease Control and Prevention (CDC). Interim US Guidance for Risk Assessment and Public Health Management of Persons with Potential 2019 Novel Coronavirus (2019-nCoV) Exposure in Travel-associated or Community Settings. Centers Dis Control Prev. 2020;2019:1–8.
26. Han Y, Yang H. The transmission and diagnosis of 2019 novel coronavirus infection disease (COVID-19): A Chinese perspective. J Med Virol. 2020;92(6):639–44. doi:10.1002/jmv.25749
27. Shen Y, Li C, Dong H, Wang Z, Martinez L, Sun Z, et al. Community outbreak investigation of SARS-CoV-2 transmission among bus riders in Eastern China. JAMA Intern Med. 2020;180(12):1665–71. doi:10.1001/jamainternmed.2020.5225

Original Article

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Comparison of Coagulation Parameters between Severe and Non-severe COVID-19 Patients Treated in a Tertiary Hospital in Indonesia

Pandji Irani Fianza,[1] Delita Prihatni,[2] Dasep Bambang Purnama[3]

[1]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine Universitas Padjadjaran-Dr.Hasan Sadikin General Hospital, Bandung, Indonesia
[2]Department of Clinical Pathology, Faculty of Medicine Universitas Padjadjaran-Dr.Hasan Sadikin General Hospital, Bandung
[3]Department of Internal Medicine, Faculty of Medicine Universitas Padjadjaran-Dr.Hasan Sadikin General Hospital, Bandung

Article History

Received: August 24, 2022
Accepted: October 04, 2023
Published: October 30, 2023

DOI: 10.15850/ijihs.v11n2.2967
IJIHS. 2023;11(2):107–111

Correspondence:
Dasep Bambang Purnama, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
Email: sundatea12@gmail.com

Abstract

Objective: To determine the differences in coagulation features in patients with severe versus non-severe COVID-19.

Method: During the period of the study from July 2020 to June 2021, 371 COVID-19 patients were treated at Dr. Hasan Sadikin General Hospital Bandung, Indonesia. These patients were divided into two groups based on the WHO criteria into severe COVID-19 with clinical signs such as severe acute respiratory syndrome to respiratory failure and non-severe cases with no respiratory symptoms. Data analyzed were Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), International Normalized Ratio (INR), fibrinogen, D-dimer, and platelet count.

Results: Median INR was significantly higher in patients with severe cases than in non-severe cases (1.04 vs. 0.94, p<0.001), which was also true for median PT (12.3 vs. 12.0 sec, p=0.030) and median fibrinogen (522 vs. 428.5 mg/dL, p=0.004). Similarly, the median D-dimer was significantly higher in severe patients (1.91 vs. 0.75 mg/dl, p<0.001). Median aPTT and platelet count were in normal limits for both severe and non-severe COVID-19 patients (28.6 vs. 29.15 sec, p>0.652 and 246 vs. 242 $x10^3/mm^3$, p>0.924, respectively).

Conclusions: The INR, PT, fibrinogen, and D-dimer can be considered as features that can be used to predict the severity of the disease and to choose the proper treatment for COVID-19 patients.

Keywords: Coagulopathy disorders, COVID-19, severe acute respiratory syndrome, non-severe acute respiratory syndrome

Introduction

The Coronavirus Disease 2019 (COVID-19) is declared a global pandemic by the WHO in March 2020. Even though the pandemic status has ended, the disease is still a global problem, including Indonesia, especially because it leads to severe complications, deathd, and prolonged consequences. Findings from everal previous studies have demonstrated that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2)—which is widely expressed in various human tissues such as lungs, gastrointestinal tract, hearth, kidney, and blood vessel endothelium—as a receptor at the cellular level to facilitate the infection process. These tissues serve as the entry points for SARS-CoV-2 infection and replication through a direct cytopathic effect.[1-3] The clinical manifestations of this disease include a broad spectrum, starting from mild symptoms to severe symptoms such as Acute Respiratory Distress Syndrome (ARDS), multiple organ failure, COVID-19 Associated Coagulopathy

(CAC), and death.

COVID-19 Associated Coagulopathy or CAC is associated with disease morbidity and mortality. The most common manifestation of CAC is venous thromboembolism (VTE), such as deep vein thrombosis (DVT) or pulmonary embolism (PE). The high incidence of VTE in COVID-19 patients reveals the importance of coagulation parameter examinations to make a diagnosis and, eventually, treat the patient.[4-8] This coagulation parameter is a quantitative parameters used to assess the progression of COVID-19. These parameters consists of D-dimer, platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized number (INR), and fibrinogen.[8, 9] Understanding these parameters will enable the clinicians to differentiate between severe and non-severe COVID-19 that will lead to accurate and quick diagnosis and proper treatment. This study was conducted to determine the differences in coagulation parameters between severe and non-severe COVID-19 in patients treated in Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

Methods

This was a retrospective analytical descriptive study using the medical records of COVID-19 patients treated in Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, during the period of June 2020 to July 2021. The sample of this study were medical records from 317 COVID-19 patients, divided into two groups of severe and non-severe COVID-19. The inclusion criteria were age over 18 years with severe and non-severe COVID-19. Patients with severe COVID-19 were defined as those having clinical signs of severe acute respiratory syndrome to respiratory failure. Meanwhile, non-severe patients were patients with no respiratory symptom COVID-19 according to the WHO criteria. Exclusion criteria are patient with previous anticoagulant treatment and those with hemostasis disorders, autoimmune disease, and neoplasm. Pregnant patients were also excluded. Data collected were analyzed using the Mann-Whitney test. This study has been approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General

Table 1 Subject Characteristics

Variable	Group		p-value
	Severe COVID-19 n=99	Non-severe COVID-19 n=218	
Age (years old), median (min-max)	57 (29–89)	52 (19–88)	<0.001[a]*
Gender, n (%)			
Female	43 (43.4)	109 (50.0)	0.278[b]
Male	56 (56.6)	109 (50.0)	
Comorbidities, n (%)			
Yes	75 (75.8)	112 (51.4)	<0.001[b]*
No	24 (24.2)	106 (48.6)	
Type of Comorbidity, n (%)			
Hypertension	45 (45.5)	61 (28.0)	0.002[b]*
Diabetes Mellitus	26 (26.3)	34 (15.6)	0.025[b]*
Cardiovascular Disease	17 (17.2)	14 (6.4)	0.003[b]*
Chronic Kidney Disease	6 (6.1)	6 (2.8)	0.202[c]
Chronic Pulmonary Disease	4 (4.0)	4 (1.8)	0.263[c]
Neurological Disease	3 (3.0)	3 (1.4)	0.381[c]
Liver Disease	2 (2.0)	1 (0.5)	0.231[c]
Rheumatic Disease	1 (1.0)	1 (0.5)	0.528[c]
HIV/AIDS	0 (0.0)	1 (0.5)	1.000[c]

[a]Mann Whitney test, [b]Chi Square test, [c]Fisher Exact test, * p<0.05

Table 2 Coagulation Parameters and the Clinical Outcomes

Variable	Groups		*P* value
	Severe COVID-19 n=99	Non-severe COVID-19 n=218	
Laboratory, median (min-max)			
Days of illness (th days)	8 (5–10)	6 (3–9)	0.001[a]*
INR	1.04 (0.93–1.14)	0.94 (0.89 –1.00)	<0.001[a]*
PT (seconds)	12.3 (11.0–14.2)	12.0 (10.5–13.6)	0.030[a]*
aPTT (seconds)	28.6 (24.3–34.7)	29.15 (24.8–33.0)	0.652[a]
Fibrinogen (mg/dL)	522 (350–680)	428.5 (329–564)	0.004[a]*
D-Dimer (mg/dL)	1.91 (0.80–9.57)	0.75 (0.40–1.82)	<0.001[a]*
Platelet (x10^3/mm^3)	246 (172–309)	242 (179–307)	0.924[a]
Outcome, n (%)			
Survival	62 (62.6)	203 (93.1)	<0.001[b]*
Death	37 (37.4)	15 (6.9)	

Median (IQR), [a]uji Mann Whitney, [b]uji Chi-Square, * p<0.05

Hospital, Bandung, Indonesia, under the ethical clearance No. LB.02.01/X.6.5/323/2021.

Results

Subject who met the inclusion and exclusion criteria were divided into two groups based on their severity of disease (99 patients with severe COVID-19 patients and 218 patients with non-severe COVID-19). The primary characteristics of the patients are described in Table 1.

Based on the data in Table 1, age, presence of comorbidities, as well as hypertension, diabetes mellitus, and cardiovascular disease as commorbidities are significantly different between the two groups (p<0.05). The median age of severe COVID-19 patients was 57 years old (range: 29–89 years old), while the median for non-severe COVID-19 patients were 52 years old(range: 19–88 years old). Severe COVID-19 patients had more comorbidities than non-severe COVID-19 patients (75.8% vs. 51.4%, p<0.001). Of all patients in severe COVID-19 group with comorbidities, 45.5% suffered from hypertension, 26.3% experienced diabetes mellitus (DM), and 17.2% had cardiovascular disease (CVD). In contrast, the majority of patients in the non-severe COVID-19 group with commorbidities had hypertension (28.0%), followed by DM (15.6%) and CVD (6.4%).

Table 2 presents the significant differences in days of illness, INR, PT, Fibrinogen, D-Dimer, and patient outcomes between the two groups (p<0.05). The median illness day of the severe COVID-19 group was higher than that of the non-severe COVID-19 group (p=0.001). The median INR and PT of the severe COVID-19 group were significantly higher than the non-severe COVID-19 group with p<0.001 and p=0.030, respectively. The severe COVID-19 group had median fibrinogen and D-dimer levels that were higher than in the non-severe COVID-19 group (p=0.004 and p<0.001, respectively). The mortality percentage in the severe COVID-19 group was higher than in the non-severe COVID-19 group (p<0.001).

Discussion

During the peak of the COVID-19 pandemic, the number of new cases increased sharply from day to day, accompanied by the identification of varying manifestations of disease. The basic pathogenesis of coagulopathy in COVID-19, as described in the Virchow's Triad theory, consists of three pathological processes of endothelial injury/damage, hypercoagulable state, and stasis. Endothelial damage occurs due to the direct invasion of the SARS-CoV-2 virus through the ACE2 receptor, the effects of pro-inflammatory cytokines, the release of various acute phase proteins, and the activation of the complement system, as well as the use of various intravascular catheters that stimulate

local inflammation. Stasis conditions, such as observed in patients with severe symptoms in the intensive care unit, prevents smooth blood flow in the blood vessels so that coagulation factors may concentrate in one location and then be activated, stimulating thrombosis.[10] In this study, clinically day off illness and survival date were significantly different in the two groups. All coagulation marker parameters increased in the severe group when compared to the non-severe Covid 19 group. These results aligned with previous studies.[11-14] Many patients infected with COVID-19 have mild or even no symptoms while some patients develop severe and critical cases that lead to multi-organ failures, including respiratory failure that will eventually lead to death if not treated properly. Inflammation, as well as immune system responses, play an important role in the pathophysiology of COVID-19, which is characterized by a significant increase in levels of pro-inflammatory cytokines.[10] In COVID-19, local and systemic inflammations cause a hypercoagulable state that eventually will lead to the disruption of the coagulation and fibrinolysis system balance. Hypercoagulation and hypofibrinolysis will trigger thrombosis in COVID-19 patients. Since a lot of ACE2 receptors are utilized by SARS-COV-2 to invade the human tissues, there is less ACE2 receptors available for angiotensin II (AT-II), and hence more AT-II is circulated. The virus and AT-II will together increase the production of plasminogen activator inhibitor 1 (PAI-1), which will establish a systemic pro-coagulant environment in the patients' circulation.[10] In COVID-19, the identification parameters or markers to predict disease progression is very important. Coagulation parameters are one of the markers to predict disease progression when the patient is admitted to the hospital. In this study, the median of aPTT in the two groups were not significantly different and was in a normal state. These results align with a past study in China which shows similar results.[15] On the other hand, PT and INR in severe COVID-19 patients are significantly higher than in the non-severe patients. Endothelial damages in COVID-19 exposes subendothelial tissue factor (TF) which will activate the extrinsic coagulation pathway. Furthermore, the tissue factor pathway inhibitor (TFPI), which inhibits the extrinsic coagulation pathway, is impaired by COVID-19. These mechanisms may explain why PT and INR, depicting the extrinsic coagulation pathway, are affected more significantly than aPTT which depicts the internal coagulation pathway.[12] The median of fibrinogen levels in the severe COVID-19 patients in this study was higher than in non-severe patients. Fibrinogen is one of acute-phase proteins synthesized by the liver as a response to stimulations from inflammatory cytokines and is involved in fibrin production of the final step of coagulation activity and its level increases in a hypercoagulable state.[13,14.] The median of D-dimer in the severe group was significantly higher than in the non-severe group. D-dimer is a specific cross-linked fibrin degradation product. D-dimer levels depict the process of fibrinolysis which will increase in a hypercoagulable state. D-dimer levels will increase as the severity of COVID-19 increases. D-dimer is one of the most established parameters used in monitoring hypercoagulable state in COVID-19.[12,14] The median platelet count of the two groups was still within normal limits. In contrast, several multicenter studies showed a higher incidence of thrombocytopenia in severe COVID-19 patients than in non-severe COVID-19 patients. The difference in the time when the platelet count is performed, in the beginning or middle of hospitalization, could cause this difference.[15, 16]

Some potential confounding factors in this study, such as liver and kidney diseases, were not analyzed, so parameter values do not fully depict coagulopathy merely due to COVID-19. In conclusion, INR, PT, fibrinogen, and D-dimer values increase significantly in severe COVID-19 cases and can be considered as a predictor of the severity of the disease and in choosing the appropriate treatment for COVID-19 patients. Thus, INR, PT, fibrinogen, and D-dimer measurements should be considered when predicting the severity of the disease and to choose the right treatment for COVID-19 patients.

References

1. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. 2021. Available from: https://covid19.go.int/.
2. Badan Nasional Penanggulangan Bencana. Tingkat Kematian (CFR) Covid-19 Indonesia. 2021. Available from: https://bnpb.go.id/.
3. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of

ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631–7. doi:10.1002/path.1570
4. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433. doi:10.1016/j.jaut.2020.102433
5. Soeroto AY SP, Pranggono EH, Kulsum ID, Suryadinata H,. Pedoman diagnostik dan pengobatan COVID-19. Indones J Chest Crtitical Emerg Med. 2020;1:7.
6. Mackman N, Antoniak S, Wolberg AS, Kasthuri R, Key NS. Coagulation abnormalities and thrombosis in patients infected with SARS-CoV-2 and other pandemic viruses. Arterioscler Thromb Vasc Biol. 2020;40(9):2033–44. doi:10.1161/ATVBAHA.120.314514
7. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020;191:9–14. doi:10.1016/j.thromres.2020.04.024
8. Dahler C, Rechner GA, Mitsios JV. Pathophysiology of COVID-19-associated coagulopathy and its impact on laboratory measures of coagulation. J Pathogen. 2021:30.
9. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. J Thromb Thrombolysis. 2020;50(1):54–67. doi:10.1007/s11239-020-02134-3
10. Lazzaroni MG, Piantoni S, Masneri S, et al. Coagulation dysfunction in COVID-19: The interplay between inflammation, viral infection and the coagulation system. Blood Rev. 2021;46:100745. doi:10.1016/j.blre.2020.100745
11. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13. doi:10.1016/S0140-6736(20)30211-7
12. Loo J, Spittle DA, Newnham M. COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. Thorax. 2021;76(4):412–20. doi:10.1136/thoraxjnl-2020-216243
13. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020;7(6):e438–e440. doi:10.1016/S2352-3026(20)30145-9
14. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. J Thromb Haemost. 2020;18(9):2103–9. doi:10.1111/jth.14975
15. Kim ES, Chin BS, Kang CK, et al. Clinical course and outcomes of patients with severe acute respiratory syndrome coronavirus 2 infection: a preliminary report of the first 28 patients from the Korean Cohort Study on COVID-19. J Korean Med Sci. 2020;35(13):e142. doi:10.3346/jkms.2020.35.e142
16. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta. 2020;506:145–8. doi:10.1016/j.cca.2020.03.022

Original Article

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Correlation between Acute Phase Symptoms with Neurological Long Covid Symptoms on COVID-19 Survivors

Ahmad Rizal Ganiem, Siuliyanty, Anam Ong, Uni Gamayani, Lisda Amalia, Yusuf Wibisono

Department of Neurology, Faculty of Medicine, Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Article History

Received: February 02, 2023
Accepted: October 25, 2023
Published: October 30, 2023

DOI: 10.15850/ijihs.v11n2.3215
IJIHS. 2023;11(2):112–119

Correspondence:
Ahmad Rizal Ganiem,
Department of Neurology
Faculty of Medicine, Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia.
Email: rizalbdg@gmail.com

Abstract

Objective: To investigate prolonged neurological impacts of COVID-19 and establish a connection between initial COVID-19 symptom severity and chronic fatigue syndrome (CFS) development, poor sleep quality (PSQ), and cognitive impairment (CI) in individuals recovered from COVID-19.

Methods: This cross-sectional study recruited COVID-19 survivors at Dr. Hasan Sadikin General Hospital Bandung, Indonesia, between June and December 2021. All participants gave informed consent and underwent interviews on demography, clinical features, long-COVID questionnaire, and neurological examination. Participants underwent cognitive examination (MOCA-INA), Chalder Fatigue Scale and Pittsburgh Sleep Quality Index (PSQI) to assess CI, CFS, and PSQ variables. Chi-Square analysis was performed to determine the probability of neurological long COVID-19 syndrome manifestations using SPSS 24.0.

Results: Of the 127 participants recruited, 67.7% were women, median (IQR) age of 33 (21–65) years, and time from hospitalization to examination of nine months (1–13). The most common neurological Long COVID symptoms were PSQ (59.8. %), CFS (51.2%), and CI (33.9%). Participants with more than five acute phase COVID-19 symptoms had a higher probability of CFS and CI (OR 2.38 (1, 16-4.9, CI 95%); OR 2.20 (1.01-4.79, CI 95%)) than those with less than five symptoms. The study did not find a significant correlation between sleep quality and number of acute-phase COVID-19 symptoms (OR 1.56 (0.76-3.20, CI 95%)).

Conclusion: Almost two-thirds of the COVID-19 survivors experienced PSQ, more than half had CFS, and almost one-third had CI. The study revealed an increasing likelihood of CFS and CI in COVID-19 survivors as the number of acute COVID-19 symptoms increases.

Keywords: Chronic fatigue syndrome, cognitive impairment, long covid, poor sleep quality

Introduction

The COVID-19, also known as Coronavirus Disease-19, is an illness caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Initially identified in Wuhan, China, in 2019, it rapidly spread to numerous countries, leading the need for the World Health Organization (WHO) to declare a pandemic in early 2020. While the respiratory tract is primarily affected by this disease, it can also have an impact on various other organs, including both the central and peripheral nervous systems.[1] According to the World Health Organization (WHO) data available until May 2021, the global number of confirmed COVID-19 cases stood at 159 million, with a reported death toll of 3.3 million, resulting in a fatality rate of 2.1%. In the case of Indonesia, the COVID-19 death rate

was higher than the global average, reaching 2.7%.[2,3] The full range of health outcomes related to COVID-19 is still not completely understood. However, approximately 35% of individuals who have recovered from COVID-19 report not fully returning to their pre-illness state within 2–3 weeks after being declared cured. In cases where individuals have experienced severe pneumonia as a result of COVID-19, it may take six months or even longer for their breathing to return to normal. Furthermore, this prolonged disability can also affect the functioning of the heart and brain.[1,4] In neurology, many COVID-19 survivors report fatigue, sleep disturbances, and cognitive impairment symptoms. Patients with cognitive impairment tend to describe complaints of "brain fog," causing behavioural fluctuations that can be frustrating for patients and healthcare professionals and fatigue. This situation is called "Long COVID." An additional factor to consider is whether, in the long term, chronic subclinical inflammation can lead to accelerated aging both peripherally and as a neurodegenerative process. [4]

The exact cause of "Long COVID" is still not fully understood, but it is believed to involve potential cellular damage caused by the virus itself and the ongoing production of inflammatory cytokines by the immune system, even after the virus is no longer present. Emerging evidence has suggested that COVID-19 patients with Long COVID may experience brain injury, which aligns with the virus's ability to infect the central nervous system (CNS). However, the clinical manifestations, frequency of CNS effects, and specific mechanisms underlying the neurological damage caused by SARS-CoV-2 infection are not well-established and require further research. Therefore, the objective of this study was to provide an overview of the long-term neurological effects and explore the relationship between the number of acute-phase COVID symptoms and Long COVID symptoms in survivors of COVID-19.

Methods

This cross-sectional study was conducted at the Neurology Outpatient Clinic of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, between January – June 2022. We invited survivors of COVID-19 infection who had been hospitalized in this hospital during the period of June–December 2021. Inclusion criteria were (1) aged 18 to 65 years, (2) had confirmed COVID-19 infection based on the result of the reverse transcription real-time polymerase chain reaction (RT-PCR) from nasal swabs, (3) had recovered from COVID-19, either confirmed negative by RT-PCR from nasal swabs, or had undergone mandated isolation period for a minimum of 14 days, (4) had undergone at least grade 3 Elementary School, (5) domiciled in the city of Bandung and its surroundings and (6) willing to complete questionnaires. Subjects with previous medical history (stroke, diabetes, cardiovascular disease, sleep disorder, and psychological disorders) were excluded from the study. The research ethical approval was obtained from the ethics committee of Hasan Sadikin Hospital (ethical clearance number: LB.02.01/X.6.5/231/2021). Global function examination with the Montreal Cognitive Assessment Indonesia (MoCA-Ina) is the value obtained by adding up all existing domains with a score range of 0-30, then grouped based on cognitive scores.[5] The questions examined the followings: visuospatial, executive function, naming, memory, attention, delayed recall, language, abstraction, and orientation, and the measurement scale obtained is in the form of a categorical (ordinal) scale. Value of 24 or more is considered normal. Fatigue was evaluated by utilizing the Chalder Fatigue Scale (CFQ-11) survey, which consisted of 11 questions rated on a scale of 0 to 3.[6] The responses from these questions were combined to calculate a comprehensive score ranging from 0 to 33, with higher scores indicating more severe symptoms. The questionnaire also included two subcategories of physical exhaustion that comprised of seven items with a potential score range of 0 to 21 and mental exhaustion, consisting of four items with a possible score range of 0 to 12. The Chalder Fatigue Scale (CFQ-11) offers an alternative scoring method called the bimodal score, where each item response is divided into two categories: 0 (0–1) or 1 (2–3). These scores are then summed up to create a scale ranging from 0 to 11. Typically, the fatigue case status, distinguishing between feeling tired or not tired, was determined using this scale. The conventional threshold for categorization was set at a score of <4 for not tired and 4 or above for feeling tired. Each participant fulfilled the Indonesian Version of Pittsburgh Sleep Quality Index (PSQI, Cronbach's alpha of 0.79) to assess the sleep quality in patients over a 1-month period. PSQI consists of 19 questions, which include sleep latency, duration, efficiency, disturbances, use of sleeping medication, and daytime dysfunction.[7] The questionnaire requires the

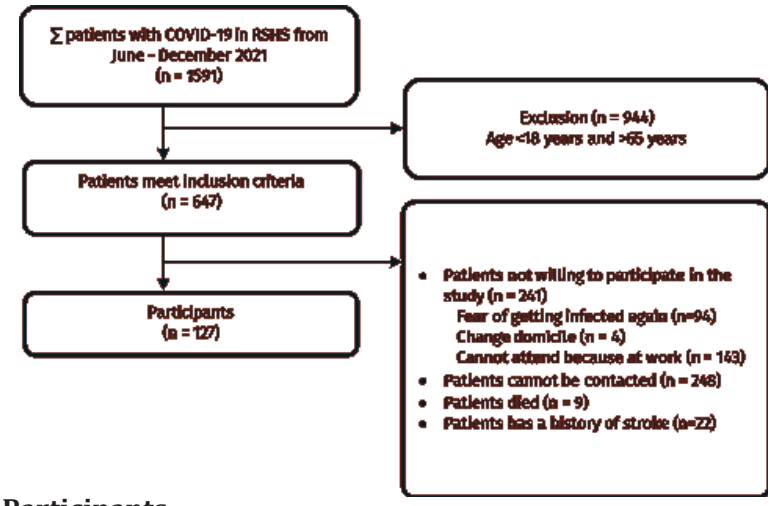

Fig. 1 Flow Chart of Participants

Table 1 Demographic Characteristics of Participants

Variable	(n=127) (%)	Median
Gender		
Male	41 (32.3)	
Female	86 (67.7)	
Age (years)		33 (21–65)
Body Mass Index (kg/m^2)		24.8 (16.2–43.5)
Underweight	4 (3.1)	
Normal	45 (35.4)	
Overweight	15 (11.8)	
Obesities	63 (49.6)	
Comorbidity		
Hypertension	11 (8.7)	
Diabetes	2 (1.6)	
Cardiovascular disease	4 (3.1)	
Chronic Obstructive Pulmonary Disorder	5 (3.9)	
Hypertension and Cardiovascular disease	3 (2.4)	
No comorbid	102 (80.3)	
Length of hospital stay (days)		14 (0–40)
ICU admission	5 (3.9)	
Length of ICU stay (days)		14 (7–20)
Time from discharge to follow-up (months)		9 (1–13)
CT Value		24 (11–38)
Number of acute phases of COVID symptoms		
≤5	54 (42.5)	
>5	73 (57.5)	

Note: Categorical characteristic data is displayed in terms of frequency and percentage, while numerical characteristics are displayed in the form of mean, standard deviation (SD), and range

patient to describe sleep patterns, such as typical bedtime and wake time, length of time taken to fall asleep, and actual sleep duration. The patient then answers a series of questions relating to sleep habits and quality. Component scores ranges from 0-3. The possible total score is within the range of 0-21 with cut-off point for poor sleep quality is higher than 5. Statistical analysis was performed with SPSS version 24.0. The normally distributed variables were expressed as mean ± standard deviation and were compared by t-test. The skewed variables were expressed as medians (IQR) and were compared by using the Mann–Whitney U-test. The Chi Square test was used to determine the relationship between long COVID symptoms and the number of acute phases of COVID symptoms.

Results

From existing records, there were 1,591 patients with COVID-19 who were treated at RSHS from June to December 2021. 944 subjects did not fulfil age criterion, leaving 647 subjects eligible for the study. Of these 647 subjects, nine people had died, 22 had a history of stroke, 248 people could not be contacted/did not give an answer, and 241 people were not willing to take part in the study for the following reasons: (1) fear of re-infection (n=94); (2) change of domicile (n=4); and (3) unable to attend due to work (n=143), so that 127 patients were available for this study (Fig. 1).

The characteristics of the research subjects comprised 32.3% men and 67.7% women, with a median age of 33 years (range: 21 – 65 years), and almost 50% were obese. Most had no comorbidity (80.3%), and the most comorbid was hypertension (8.7%). The median length of stay was 14 days (range: 0 – 40 days); 3.9% were admitted to the ICU, with the median length of stay in the ICU being 14 days. The median CT-value is 24 (range (11 –38)). Based on the number of symptoms of the acute phase of COVID, subjects who had symptoms >5 were 57.5%, and 5 were 42.5%. The basic characteristics of the research subjects can be seen in Table 1.

The median time to go home or be declared cured until the examination was nine months (range 1–13 months). All subjects completed the Long COVID questionnaire and obtained the most neurological symptoms, namely fatigue (53.9%), sleep disturbances (26.8%), muscle weakness (22.8%). Other symptoms such as joint pain, headache, myalgia, dizziness, olfactory disturbances, and taste disturbances were found in less than 10% of the subjects (Table 2).

Table 2 Characteristics of Long COVID Symptoms in Participants

Variables	Total (n=127)
Long COVID symptoms, n (%)	
Fatigue	68 (53.9)
Headache	9 (7.1)
Myalgia	4 (3.1)
Chest pain	2 (1.6)
Joint pain	10 (7.9)
Sore throat	5 (3.9)
Difficult to swallow	2 (1.6)
Low grade fever	5 (3.9)
Palpitations	8 (6.3)
Dizziness	6 (4.7)
Nasal congestion	5 (3.9)
Skin rash	5 (3.9)
Diarrhea or vomiting	6 (4.7)
Nausea	6 (4.7)
Smell disorder	11 (8.7)
Taste disorder	6 (4.7)
Decreased appetite	4 (3.1)
Sleep difficulties	34 (26.8)
Muscle weakness	29 (22.8)
Hair loss	41 (32.3)

Note: Categorical variables of Long COVID symptoms are displayed in the form of frequency (%)

The analysis results in Table 3 showed that subjects who had > 5 symptoms of acute phases COVID symptoms had more cognitive impairment than thos who had < 5 symptoms (41.1% vs 24.1%, OR: 2.20; 95% CI: 1.01–4.79; p=0.045). Chronic fatigue syndrome was also more frequently found in subjects with >5 symptoms in the acute phase of COVID-19 (60.3 vs 38.9%, OR: 2.38; 95% CI: 1.16–4.90; p=0.017). there were no significant statistical difference between those two groups with regard to sleep disturbance (Table 3).

Discussion

The study's results on 127 patients showed that COVID-19 was more common in women,

Table 3 Correlation between Cognitive Disorders, Chronic Fatigue Syndrome, and Sleep Disorders (categorical) based on the Number of Symptoms of COVID-19 in the Acute Phase

Long COVID	Total n=127	Number of Symptoms of COVID-19 in Acute Phase		p-value	OR (95% CI)
		>5 n=73	≤5 n=54		
MOCA-INA					
Cognitive impairment	43 (33.9)	30 (41.1)	13 (24.1)	0.045*	2.20 (1.01 – 4.79)
Normal	84 (66.1)	43 (58.9)	41 (75.9)		
Chalder Fatigue Scale,					
Chronic Fatigue Syndrome	65 (51.2)	44 (60.3)	21 (38.9)	0.017*	2.38 (1.16 – 4.90)
Normal	62 (48.8)	29 (39.7)	33 (61.1)		
PSQI					
Poor Sleep Quality	76 (59.8)	47 (64.4)	29 (53.7)	0.225	1.56 (0.76 – 3.20)
Normal	51 (40.2)	26 (35.6)	25 (46.3)		

Note: analysis using Chi-Square test, *p<0.05

which was 67.7%. This result is supported by similar results obtained in several other studies, which show that more women suffer from COVID-19 than men, with a relatively small percentage of 69%, 63%, and 52%.[8,9],[10] The study of Francesca Bai *et al*.[11] also revealed that women have a 3-fold higher risk of being diagnosed with Long COVID. Hormones may play a role in maintaining a hyperinflammatory state during the acute phase even after recovery, and more robust IgG antibody production in women in the early stages of the disease has been reported; this may result in a more favorable outcome in women, but may also play a role in prolonging the manifestations of the disease.The patients in this study had a median of 33 years. Several similar studies showed variations in the median age of patients suffering from Long COVID-19, namely 33, 36.5, and 39.35 years.[8],[12,13] Nearly 50% of the patients in this study were obese. Obesity is associated with chronic inflammatory conditions and a reduced immune system, increasing a person's susceptibility to infection. Therefore, obesity is an independent risk factor for the poor progression of COVID-19 disease. The mechanisms associated with disease severity in obesity are thought to occur through higher ACE-2 concentrations, chronic inflammation, and the restrictive functional capacity of the obese lung.[14] The comorbidity most often accompanies patients with COVID-19 is hypertension, which is 8.7%. Meanwhile, Huang *et al*.[16] in their study showed a higher percentage (29%) of hypertension, and research by Sanyaolu *et al*.[15] proved that hypertension was the most common comorbid (15%) in patients diagnosed with COVID-19. The investigators agree that subjects with comorbidities were associated with more severe disease outcomes when infected with SARS-CoV-2 compared to patients without previous comorbidities.[16]

This study collected data on the number of symptoms experienced by patients suffering from acute COVID-19 and the symptoms experienced by patients after being declared cured of COVID-19, including those involving neurological sequelae, with the most common symptoms being excessive fatigue, cognitive impairment, and sleep disorders.

This study results are in line with several previous studies, including those from the United States, Europe, and China, which reported the outcome of patients who had completed hospitalization in the acute phase of COVID-19. COVID-19 survivors are reported to have some persistent symptoms. In a study in the United States, 32.6% of patients still had symptoms, 55% in Europe and 76% in China. The most frequently reported symptoms were fatigue (98%), shortness of breath (93%), and headache (91%). However, many symptoms still affect other systems in the body and fluctuate from time to time. A review article of 27 studies on the post-COVID-19 syndrome showed that the most common symptoms were fatigue (47%), shortness of breath (32%), and muscle aches (25%). The study

of Graziella Orru *et al*. on the persistence of neurological and psychological symptoms also showed similar results, where the main symptoms associated with Long COVID were headache (90%), fatigue (80%), muscle pain/ myalgia (70%), articular pain (55%), cognitive impairment (59%), loss of smell (55%), and sleep disturbances such as insomnia (26%).[17,18,19] Long COVID-19 syndrome is a complication with persistent symptoms after recovery from SARS-CoV-2 infection. Guidelines published by the National Institute for Health and Care Excellence (NICE), The Scottish Intercollegiate Guidelines Network, and the Royal College of General Practitioners define long COVID-19 as signs and symptoms that develop during or after COVID-19-related illness and persist for more than four weeks without being supported by another diagnosis. Two main symptom groups of long COVID have been identified: (1) a group consisting only of fatigue, headache, and upper respiratory tract complaints; and (2) the group with multi-system complaints including fever and gastroenterological symptoms.[20,21] Studies linking the number of symptoms experienced during acute conditions with long COVID-19 have been carried out previously. According to Sudre *et al*.,[21] more than five symptoms in the first week of acute infection were significantly associated with the development of long COVID-19 regardless of age or gender. In this study, long COVID symptom indicators were expressed by several scoring systems for cognitive impairment, CFS, and sleep disorders.

As assessed by the Chalder Fatigue Scale, the number of acute phase COVID-19 symptoms was significantly associated with CFS. A study by Stavem *et al*. also demonstrated that CFS rates were higher in patients with severe symptoms during acute COVID-19 based on three different scoring systems. The study's results by Goertz *et al*.[22] also support this finding by suggesting that the number of symptoms present during initial infection was the most potent factor in predicting the number of symptoms at three months.[23] Chronic fatigue syndrome is defined as fatigue, post-activity malaise, sleep disturbance, cognitive impairment, as well as persistent unprovoked pain lasting six months or more of sufficient intensity, not fully explained by any medical condition. This condition can be observed after some viral and bacterial infections. There is also an association between CFS and depression, although it remains unclear whether one diagnosis precedes the onset of another.[24] Symptoms of CFS can be caused by damage to multiple organ systems during the acute phase of COVID-19, causing impaired heart, lung, or kidney function. The overall inflammatory state increased inflammatory mediators, and activation of cell-mediated immunity may contribute to a CFS-like state. Disruption of routine activities due to ongoing post-COVID-19 draining symptoms, social isolation, and post-traumatic syndrome due to severe illness requiring mechanical ventilation can lead to depression, which can sometimes trigger CFS. Endocrine dysfunction leading to hypocortisolism, hypothyroidism, or disruption of the hypothalamus-pituitary-adrenal (HPA) axis may also be another potential explanation for CFS.[24] In this study, it was found that there was a significant relationship between the number of acute phase COVID-19 symptoms and cognitive impairment as measured by MoCA-Ina. This result is similar to that was observed by Jessica *et al*., who did a follow-up of up to 12 months on 96 COVID-19 survivors and found that only 22.9% of patients were completely symptom-free, and one of the symptoms persisted until the 12th month was neurocognitive symptoms. The cause of some patients experiencing long-term symptoms after COVID-19 remains unclear, but a potential cause for differences in post-infection outcome is viral load and host factors such as genetic susceptibility or induction of anti-inflammatory cells. The development of IgA ANA autoantibodies and high titers of serum IgG antibodies targeting the GD1b ganglioside have been found in certain neurologic affected patients. A study by Miskowiak *et al*.[25] observed the trajectory of cognitive functions from 3 months to 1 year after hospitalization with COVID-19, indicating that patients with impaired cognition three months after hospitalization do not improve after one year, while patients with no impairments after three months remain cognitively normal. This is consistent with meta-analytic analysis by Ceban *et al*. that suggested that patients' cognitive impairments after COVID-19 persist over time. However, this is contradicted by the results of a study conducted by Alemanno *et al*., who reported a high prevalence of cognitive impairment during the acute phase of COVID-19; examination at follow-up one month after discharge found that the total MoCA and Mini-Mental Status Examination (MMSE) scores were significantly higher than at admission. This indicates that cognitive impairment is more severe during the acute phase of

COVID-19 than in the acute post-COVID-19 phase.[26] This study discovered that COVID-19 survivors with some acute phase COVID symptoms >5 experienced sleep disturbances but were not statistically significant. Several previous studies have shown that the number of symptoms of the acute phase of COVID is associated with decreased sleep quality in COVID-19 survivors. The increased number of symptoms of the acute phase of COVID is closely related to the severity of COVID. The severity of COVID-19 is related to a cytokine storm mediated by IL-6, thereby increasing the permeability of the blood-brain barrier causing activation of glial cells, producing inflammatory cytokines, and resulting in sleep disturbances. In this study, the results were not statistically significant, possibly because the cutoff score for the PSQI was too low. The study of Fernández-de-las-Peñas *et al*.[26] in Spain with a Caucasian population getting a PSQI cut of 8 showed a statistically significant difference in sleep quality in Long COVID patients. Vitale *et al*.[28] conducted a study on four COVID-19 survivors that aimed to objectively assess the consequences of the severity of COVID-19 on sleep quality using actigraphy. Research subjects who experience severe COVID-19 degrees and require extended ICU care have the potential to affect sleep quality results, so it is concluded that there is a relationship between ICU care and poor sleep quality. On the other hand, the administration of necessary sedation during mechanical ventilation may play a role in decreasing sleep quality and disrupting sleep habits. Meanwhile, COVID-19 survivors treated in the ICU in this study were only 3.9%, so it did not produce a significant relationship.[23,24,25]

There are some limitation in this study. First, PSQI is a subjective questionnaire, so objective sleep measures are necessary to make a definite diagnosis and to clarify the presence or absence of other sleep disorders causative for the participants' subjective disturbance in sleep maintenance. Second, this study assessed cognitive impairment using MOCA-INA as a screening tools that could not describe the specific cognitive subdomain in Long COVID. Third, this study did not collect laboratory data (cytokines, d-dimer, CRP, fibrinogen, procalcitonin) for patients during the acute phase of COVID. This study shows that almost two-thirds of COVID-19 survivors at this hospital experienced sleep quality disorders, more than half experienced chronic fatigue syndrome, and almost a third experienced cognitive disorders. There is a significant relationship between the number of symptoms of more than five during the acute phase of COVID-19 with chronic fatigue syndrome and cognitive impairment. Sleep disturbances were more common in COVID-19 survivors with more than five acute-phase COVID symptoms but were not statistically significant.

References

1. DeKosky ST, Kochanek PM, Valadka AB, Clark RSB, Chou SH, Au AK, et al. Blood Biomarkers for Detection of Brain Injury in COVID-19 Patients. J Neurotrauma. 2021;38(1):1–43. doi:10.1089/neu.2020.7332
2. WHO. WHO COVID-19. WHO; 2021. Available from: https://covid19.who.int/?gclid=CjwKCAiA9vOABhBfEiw.
3. Satuan Tugas Penanganan COVID-19. Peta Sebaran COVID-19 [Internet]. 2021. https://covid19.go.id/peta-sebaran-covid19. Available from: Available from: https://covid19.go.id/peta-sebaran-covid19.
4. Morley JE. Editorial: COVID-19 - The Long Road to Recovery. J Nutr Health Aging. 2020;24(9):917–9. doi:10.1007/s12603-020-1473-6
5. Rambe AS, Fitri FI. Correlation between the Montreal Cognitive Assessment-Indonesian Version (Moca-INA) and the Mini-Mental State Examination (MMSE) in Elderly. Open Access Maced J Med Sci. 2017;5(7):915–9. doi:10.3889/oamjms.2017.202
6. Jackson C. The Chalder Fatigue Scale (CFQ 11). Occup Med (Lond). 2015;65(1):86. doi:10.1093/occmed/kqu168
7. Setyowati A, Chung MH. Validity and reliability of the Indonesian version of the Pittsburgh Sleep Quality Index in adolescents. Int J Nurs Pract. 2021;27(5):e12856. doi:10.1111/ijn.12856
8. Wang Y, Sibaii F, Lee K, J. Gill M, L. Hatch J. NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice. 1. medRxiv. 2021;1(165):1–13.
9. Del Brutto OH, Rumbea DA, Recalde BY, Mera RM. Cognitive sequelae of long COVID may

not be permanent: A prospective study. Eur J Neurol. 2022;29(4):1218–21. doi:10.1111/ene.15215
10. Liu YH, Wang YR, Wang QH, Chen Y, Chen X, Li Y, et al. Post-infection cognitive impairments in a cohort of elderly patients with COVID-19. Mol Neurodegener. 2021;16(1):1–10.
11. Bai F, Tomasoni D, Falcinella C, Barbanotti D, Castoldi R, Mulè G, et al. Female gender is associated with long COVID syndrome: a prospective cohort study. Clin Microbiol Infect. 2022;28(4):611.e9-611.e16. doi:10.1016/j.cmi.2021.11.002
12. Desdiani D, Sutarto AP, Kharisma AN, Safitri H, Hakim AF, Rusyda SH. Sequelae in COVID-19 patients 3 months after hospital discharge or completion of self-isolation. Health Sci Rep. 2021;4(4):e444. doi:10.1002/hsr2.444
13. Dennis A, Wamil M, Alberts J, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ Open. 2021;11(3):e048391. doi:10.1136/bmjopen-2020-048391
14. Tamara A, Tahapary DL. Obesity as a predictor for a poor prognosis of COVID-19: A systematic review. Diabetes Metab Syndr. 2020;14(4):655–9. doi:10.1016/j.dsx.2020.05.020
15. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its Impact on Patients with COVID-19. SN Compr Clin Med. 2020;2(8):1069–76. doi:10.1007/s42399-020-00363-4
16. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220–32. doi:10.1016/S0140-6736(20)32656-8
17. Zapatero DZ, Hanquet G, Heede K Van Den. Epidemiology of long COVID: a pragmatic review of the literature. KCE. 2021;1–16.
18. Aiyegbusi OL, Hughes SE, Turner G, Rivera SC, McMullan C, Chandan JS, et al. Symptoms, complications and management of long COVID: a review. J R Soc Med. 2021;114(9):428–42. doi:10.1177/01410768211032850
19. National Institute for Health and Care Excellence (NICE) SIGN (SIGN) and RC of GP (RCGP). Covid19-Rapid-Guideline-Managing-the-Longterm-Effects-of-Covid19-Pdf-51035515742. 114 Publ 01032022. 2022;1–106.
20. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601–15. doi:10.1038/s41591-021-01283-z
21. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Prevalence and determinants of fatigue after covid-19 in non-hospitalized subjects: a population-based study. Int J Environ Res Public Health. 2021;18(4):2030. doi:10.3390/ijerph18042030
22. Goërtz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome?. ERJ Open Res. 2020;6(4):00542–2020. doi:10.1183/23120541.00542-2020
23. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One. 2020;15(11):e0240784. doi:10.1371/journal.pone.0240784
24. Seeßle J, Waterboer T, Hippchen T, Simon J, Kirchner M, Lim A,, et al. Persistent symptoms in adult patients 1 year after coronavirus disease 2019 (COVID-19): a prospective cohort study. Clin Infect Dis. 2022;74(7):1191–8. doi:10.1093/cid/ciab611
25. Miskowiak KW, Fugledalen L, Jespersen AE, Sattler SM, Podlekareva D, et al. Trajectory of cognitive impairments over 1 year after COVID-19 hospitalisation: Pattern, severity, and functional implications. Eur Neuropsychopharmacol. 2022;59:82–92. doi:10.1016/j.euroneuro.2022.04.004
26. Fernández-de-Las-Peñas C, Torres-Macho J, Elvira-Martínez CM, Molina-Trigueros LJ, Sebastián-Viana T, Hernández-Barrera V. Obesity is associated with a greater number of long-term post-COVID symptoms and poor sleep quality: A multicentre case-control study. Int J Clin Pract. 2021;75(12):e14917. doi:10.1111/ijcp.14917
27. Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, et al. Cytokine Storm in COVID-19-immunopathological mechanisms, clinical considerations, and therapeutic approaches: The REPROGRAM consortium position paper. Front Immunol. 2020;11:1648. doi:10.3389/fimmu.2020.01648
28. Vitale JA, Perazzo P, Silingardi M, Biffi M, Banfi G, Negrini F. Is disruption of sleep quality a consequence of severe Covid-19 infection? A case-series examination. Chronobiol Int. 2020;37(7):1110–14. doi:10.1080/07420528.2020.1775241

Case Report

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Crowned Dens Syndrome: A Rare Cause of Sudden Onset Neck Pain

Nauman Ismat Butt,[1] Muhammad Bilal Rasheed,[1] Fahmina Ashfaq,[2] Aniqa Anser[1]

[1]Department of Medicine & Allied, Azra Naheed Medical College, Superior University Lahore, Pakistan
[2]Department of Medicine, Jinnah Hospital, Allama Iqbal Medical College Lahore, Pakistan

Article History

Received: November 05, 2022
Accepted: September 05, 2023
Published: October 30, 2023

DOI: 10.15850/ijihs.v11n2.3083
IJIHS. 2023;11(2):120–124

Correspondence:
Dr. Nauman Ismat Butt,
Department of Medicine & AlliedAzra Naheed Medical College, Superior University Lahore, Pakistan.
Email: nauman_ib@yahoo.com

Abstract

Objective: To report a case of Crowned Dens Syndrome (CDS), which is a rare disorder caused by crystal deposition by calcium pyrophosphate dihydrate in the peridontoid soft tissues surrounding the C1 and C2 vertebrae that presents in elderly with sudden onset neck pain, neck stiffness, fever, and elevated inflammatory markers, with periodontal calcification in a halo or crown configuration on radiography considered diagnostic.

Methods: A 64-year-old diabetic and hypertensive female patient presented with a 6-day history of sudden onset posterior neck pain and stiffness. Movements of the cervical spine were equally limited in all directions, causing marked aggravation of pain. There was no focal neurologic loss. Her inflammatory markers were markedly raised.

Results: Based on radiography, she was diagnosed with Crowned Dens syndrome and started on oral prednisolone, paracetamol, and tizanidine along with topical diclofenac. Oral NSAIDs were contraindicated due to her renal insufficiency.

Conclusion: Crowned Dens Syndrome (CDS) is a rare cause of neck pain. Clinicians should consider this syndrome in their differential diagnosis. Timely diagnosis and treatment of CDS will lead to avoidance of unnecessary investigations and medications in such patients, along with a reduction in the length of stay.

Keywords: Calcium pyrophosphate deposition, crowned dens syndrome, neck pain, neck stiffness

Introduction

Crowned Dens Syndrome (CDS) is a rare disorder, and was first reported in 1985 as a disorder occurring mainly in older individuals with a male-to-female ratio of 3:5. An under-recognized cause of acute neck pain and fever, CDS is a distinctive clinical syndrome linked to Calcium Pyrophosphate Deposition Disease (CPPD). CPPD, occurring mostly in articular cartilage and ligaments, is asymptomatic in 50% patients but can manifest as acute joint inflammation similar to gout, and is therefore also referred as pseudogout. CDS is caused by crystal deposition by calcium pyrophosphate dehydrate in the peridontoid soft tissues surrounding the C1 and C2 vertebrae. This generally presents in elderly with sudden onset neck pain, neck stiffness, fever and elevated inflammatory markers.[1,2] Delirium has also been reported in these elderly patients. CDS is a rare entity and little is known about its epidemiology. It is very likely that many cases of CDS are missed. Its diagnosis relies heavily on appropriate imaging. Diagnosis of CDS is based on presence of periodontal calcification above and lateral to dens of C2 vertebra in a halo or crown configuration on radiography.[3] Aspiration of local fluid collections that demonstrate calcium pyrophosphate crystals in crowned dens syndrome is the most definite means for diagnosis; however, aspirations are rarely performed clinically.[4] Advances in imaging, for example dual-energy computed

tomography that may chemically identify crystal deposition, would certainly help in CDS diagnosis.[5] Nevertheless, until such type of testing becomes easily available, it is essential that CDS be included as a differential diagnosis in clinical evaluation of patients with acute neck pain and raised inflammatory markers especially in elder patients.

In general, CDS needs medical management and anti-inflammatory medications alone is still the mainstay of treatment for this condition.[6] CDS has a good prognosis and the patients generally become asymptomatic within 4–6 weeks after initiation of therapy.[7] Majority of the patients recover without any clinical sequelae. Modification or resorption of the calcific deposits is commonly seen within 4-6 weeks or even earlier. Non-steroidal anti-inflammatory drugs (NSAIDs) are the gold standard of anti-inflammatory treatment in CDS and are given as first line therapy. NSAIDs provide rapid relief of pain generally within a few days after initiation and also reduce the blood inflammatory markers. Oral colchicine may also be prescribed in addition to NSAIDs. In severe disease or disease not responding to NSAIDs, corticosteroids such as prednisolone may be used. Furthermore, in refractory or severe cases where the symptoms persist despite medical therapy, surgical decompression and stabilization may be required, especially when there is evidence of spinal cord compression, myelopathy or cervical stenosis.[8] Herein, the report case of a patient presenting with sudden onset posterior neck pain and stiffness who was diagnosed with CDS after appropriate radiography. Although a rare cause of neck pain, it is important to diagnose CDS timely and clinicians should consider it in their differential diagnosis to avoid unnecessary investigations and medications in such patients.

Case

A 64-years old female patient was presented with 6-day history of sudden onset posterior neck pain and stiffness of moderate to severe intensity causing difficulty in neck movements. There was no history of trauma. She was a known diabetic and hypertensive for last 15 years, taking oral medicines with good compliance and good control. On examination, the patient was vitally stable with a temperature of 100°F (37.7°C). She was apprehensive due to pain but was co-operative and reported tenderness on palpation of back of neck. There were no deformity, mass or skin lesions on examination of neck and back. Movements of the cervical spine were equally limited in all directions, with no radiation of pain. However, neck movements caused marked aggravation of pain. Signs of meningeal irritation (Kerning's and Brudzinski's) were negative. There was no sensory loss; normal muscle tone, reflexes and power in both upper and lower limbs. Rest of the examination was unremarkable.

The result of the X rays of the cervical spine demonstrated calcification of para-

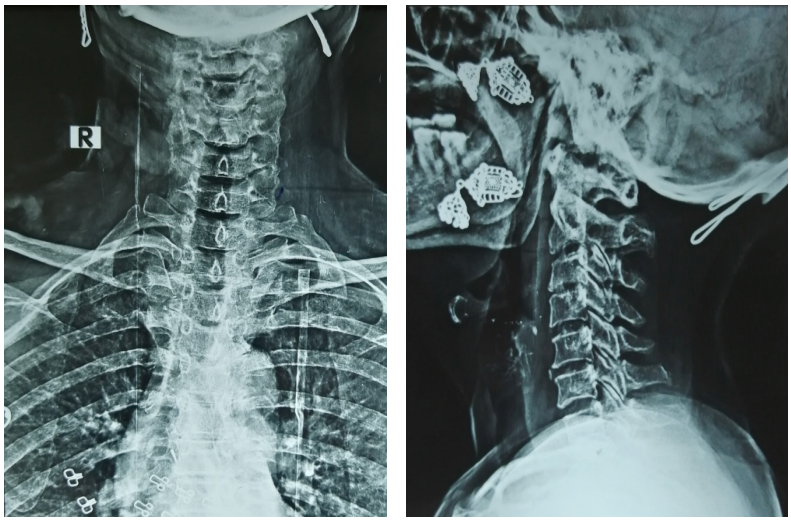

Fig. 1 X-ray Cervical Spine (AP and Lateral Views)

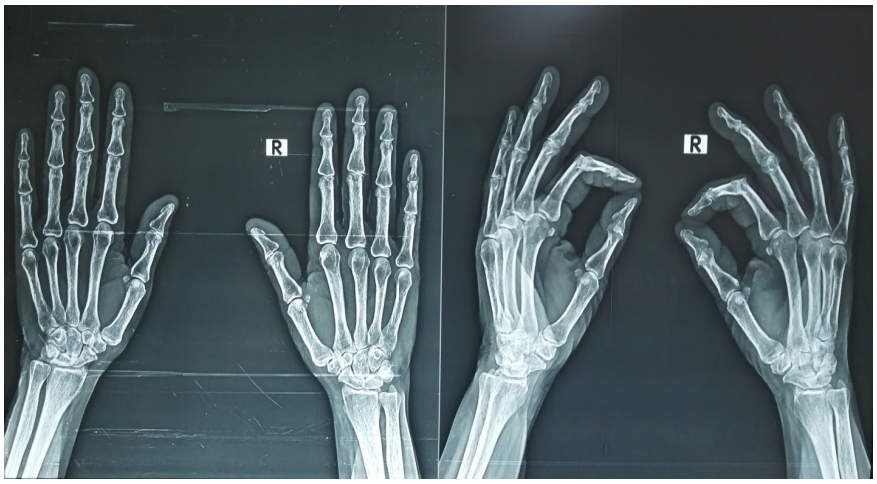

Fig. 2 X-ray Hands (AP and Oblique views)

vertebral soft tissue at C1 and C2 vertebrae, mild osteophyte formation and straightening of cervical spine as shown in Fig. 1. On further investigation, her ESR (98 mm/hour) and CRP (86 mg/dl) were markedly raised. She had moderate renal insufficiency with a creatinine clearance of 45 ml/min. Her CBC, liver profile and urinalysis were normal. HbA1c was 6.6%. Blood and urine cultures were negative. X rays of the hands demonstrated minimal joint space narrowing at 3rd and 4th PIP joints bilaterally, subtle osteophyte formation at right 3rd PIP joint and generalized reduction in bone mineral density as shown in Fig. 2.

The X rays of the knees demonstrated moderate joint space narrowing of medial compartment more of left knee and early osteophyte formation as shown in Fig. 3. The differential diagnosis included cervical spondylitis, vertebral fracture, metastatic vertebral tumor, meningitis, polymyalgia rheumatic and giant cell arteritis which were ruled out after clinical examination and investigations. Based on clinical and radiographic findings, she was diagnosed as Crowned Dens syndrome and started on oral prednisolone 10mg per day, colchicine 1mg per day, paracetamol 2gms per day and tizanidine 8mg per day along with topical diclofenac gel application. Oral NSAIDs were contraindicated due to her renal insufficiency. The patient improved and was discharged 7 days after admission with advice regarding regular follow up and tapering of oral corticosteroids.

Discussion

Crown Dens Syndrome or CDS is a rare cause

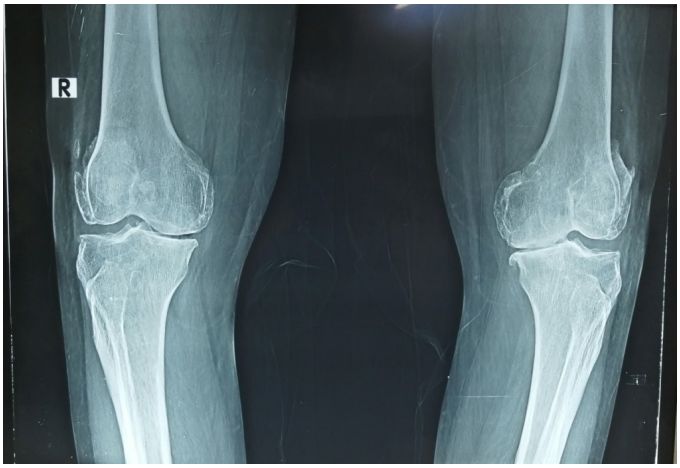

Fig. 3 X-ray Knees (AP view)

of neck pain, stiffness, fever and elevated inflammatory markers. The differential diagnosis of neck pain, stiffness and fever is quite broad and includes cervical spondylitis, vertebral fracture, metastatic vertebral tumor, meningitis, polymyalgia rheumatic and giant cell arteritis.[9] There is often a delay in diagnosis of CDS or it may be misdiagnosed entirely leading to extensive investigations, inappropriate medications and prolonged hospital stay.[9,10] CDS is not uncommon but is often misdiagnosed or ignored due to a lack of knowledge about the disease. Statistics suggest that CDS is a major cause of acute neck pain causing limited mobility accounting for up to 2% cases of acute neck pain.[11] However with adequate clinical finding and appropriate investigations the differential diagnosis may be ruled out and a diagnosis of CDS can be made timely. The current diagnostic criteria for CDS include a history of acute neck pain and limited cervical activity in addition to raised inflammatory markers such as ESR, CRP and white blood cells. Radiographic finding of CDS is presence of periodontal calcification above and lateral to dens of C2 vertebra in a halo or crown conFig.uration.[3] The limitation of X-rays is that anatomical structures surrounding odontoid process are not distinguished separately. CT scan is considered investigation of choice to identify calcification of the periodontal ligaments especially the transverse ligament of atlas cruciform ligament, apical ligament and alar ligament.[12] MRI scan does not help to diagnose calcification but is superior to see inflammatory response and spinal cord compression.[13] The definitive diagnosis relies on histological demonstration of calcium pyrophosphate crystals on biopsy.[14] However the current patient was needle phobic and refused aspiration biopsy. The incidence of CDS is associated significantly with sex and age being more prevalent in elderly females.[11,15] Oka *et al*.[16] reported that patients with CDS had a mean age 71.4 years with 60% female preponderance. Trauma, genetic factors and the co-presence of rheumatologic diseases may affect development of CDS.[11] However, there has been no proven relationship of CDS with diabetes or hypertension. Calcium Pyrophosphate crystal deposition in peripheral joints can lead to chondrocalcinosis and early osteoarthritis of these joints.[17] Performing radiographs of peripherals joints (knee, hands, and wrist) in absence of specific symptoms may demonstrate involvement of joints other than atlantoaxial joint in CDS patients. In the current patient, there was no radiographic evidence of chondrocalcinosis in joints of hands, wrists and knees. This is similar to the case reported by Lee *et al*.[18] CDS has a good prognosis and the patients generally improve with medical management encompassing anti-inflammatory drugs (NSAIDs, corticosteroids, colchicine).[19,20,] The current patient had renal insufficiency due to which NSAIDs were contraindicated. She was started on oral prednisolone 10mg per day and colchicine 1mg per day after which she reported improvement in her symptoms. Follow up was planned with an aim to taper and stop colchicine in 2 weeks and corticosteroids in 4 weeks.

In conclusion, Crowned Dens Syndrome (CDS) is a rare cause of neck pain and should be considered by clinicians in their differential diagnosis. Timely diagnosis and treatment of CDS will lead to avoidance of unnecessary investigations and medications in such patients along with a reduction in length of stay.

References

1. Deroux A. Une cervicalgie fébrile [A febrile neck pain]. Rev Med Interne. 2023;44(7):381–2. doi:10.1016/j.revmed.2023.03.003
2. Sakai D, Ono R, Ichibayashi R. Physical findings of crowned dens syndrome. Clin Case Rep. 2023;11(1):e6852. doi:10.1002/ccr3.6852
3. Awisat A, Rosner I, Rimar D, Rozenbaum M, Boulman N, Kaly L, et al. Crowned dens syndrome, yet another rheumatic disease imposter. Clin Rheumatol. 2020;39(2):571–4. doi:10.1007/s10067-019-04822-9
4. Heck A, Nolan N, Rojas-Moreno C. Crowned dens syndrome: calcium pyrophosphate deposition disease masquerading as osteomyelitis. J Rheumatol. 2018;45(10):1422–3. doi:10.3899/jrheum.170921
5. Zimmer V. Crowned dens syndrome. Clin Case Rep. 2020;8(10):2088–9. doi:10.1002/ccr3.3058
6. Bamgboje AO, Mohandas N. Crowned Dens Syndrome Masquerading as Meningitis. Cureus. 2021;13(1):e12678. doi:10.7759/cureus.12678
7. Yamada T, Saitoh T, Hozumi H, Ishikawa Y, Noguchi H, Shimada Y. Crowned dens syndrome. Acute Med Surg. 2015;2(4):273.

doi:10.1002/ams2.98
8. Oka A, Okazaki K, Takeno A, Kumanomido S, Kusunoki R, Sato S, et al. Crowned dens syndrome: report of three cases and a review of the literature. J Emerg Med. 2015;49(1):e9–e13. doi:10.1016/j.jemermed.2015.02.005
9. Michel J, Bedel JB, Pinson C, Joly LM. Crowned dens syndrome: an uncommon mimic of meningitis in the emergency department. Am J Emerg Med. 2023;63:180.e1–180.e3. doi:10.1016/j.ajem.2022.09.045
10. Igami E, Fukae J, Kanazawa K, Fuse A, Nakajima A, Eguchi H, Hattori N, et al. Two rare diseases, acute calcific retropharyngeal tendinitis, and crowned dens syndrome, mimicking meningitis: A case report. Front Neurol. 2022;13:946222. doi:10.3389/fneur.2022.946222
11. Goto S, Umehara J, Aizawa T, Kokubun S. Crowned dens syndrome. J Bone Joint Surg Am. 2007;89(12):2732-6. doi:10.2106/JBJS.F.01322
12. Ross JS, Moore KR. Diagnostic imaging: spine. US: Elsevier Health Sciences; 2015.
13. Zeng L, Liao H, Xie M, Ren F, Zhang Y, Wang Q. Images in neuroscience: crowned dens syndrome. Neurol India. 2022;70(3):1329–30. doi:10.4103/0028-3886.349617
14. Rosenthal AK. Calcium pyrophosphate deposition and crowned dens syndrome. Cleve Clin J Med. 2021;88(4):206–7. doi:10.3949/ccjm.88a.21008
15. Sano M, Yamashita S, Aiba T. The prevalence of calcification around odontoid process and the incidence of crowned dens syndrome in the neurosurgical ward: A single institution's analysis. Mod Rheumatol. 2018;28(1):182–7. doi: 10.1080/14397595.2017.1316461.
16. Oka A, Okazaki K, Takeno A, Kumanomido S, Kusunoki R, Sato S, et al. Crowned dens syndrome: report of three cases and a review of the literature. J Emerg Med. 2015;49(1):e9–e13. doi: 10.1016/j.jemermed.2015.02.005.
17. Stack J, McCarthy G. Calcium pyrophosphate deposition (CPPD) disease-treatment options. Best Pract Res Clin Rheumatol. 2021;35(4):101720. doi:10.1016/j.berh.2021.101720
18. Lee GS, Kim RS, Park HK, Chang JC. Crowned dens syndrome: a case report and review of the literature. Korean J Spine. 2014;11(1):15–7. doi:10.14245/kjs.2014.11.1.15
19. Koyfman A, Yaffe D. Crowned dens syndrome. A case report. Neuroradiol J. 2014;27(4):495–7. doi:10.15274/NRJ-2014-10056
20. Abdelkefi I, Saidenberg-Kermanac'h N, Boissier MC, Semerano L, Sigaux J. Crowned dens syndrome. Joint Bone Spine. 2022;89(1):105288. doi:10.1016/j.jbspin.2021.105288

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Case Report

Paradoxical Hemiparesis from Cerebellopontine Angle Tumor: A Case Report

James Gunawan,[1] Maula Nuruddin Gaharu[2]

[1] Faculty of Medicine, Atma Jaya Catholic University of Indonesia, Indonesia
[2] Department of Neurology, Bhayangkara Hospital TK. I R. Said Sukanto, Jakarta, Indonesia

Article History

Received: August 10, 2022
Accepted: September 09, 2023
Published: October 30, 2023

DOI: 10.15850/ijihs.v11n2.2947
IJIHS. 2023;11(2):125–128

Correspondence:
James Gunawan,
Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia
Email: mesgunawan@gmail.com

Abstract

Objective: To report a vestibular schwannoma in the cerebellopontine angle presenting with paradoxical hemiparesis with the Kernohan-Woltman Notch Phenomenon (KWNP).

Methods: A 31-year-old female presented to the neurology clinic at Bhayangkara Hospital TK. I R. Said Sukanto, Indonesia, on 29 November 2021 with loss of balance, hearing, vision, and weakness in her left arm and leg. On physical examination, the patient had reduced left arm and leg muscle strengths against resistance (MRC grade 4), face deviation to the left, abnormal finger-to-nose test, dysdiadochokinesia, and inability to perform tandem gait. She was admitted for a brain MRI but did not return to the hospital for re-evaluation and surgery.

Results: The brain MRI showed a mass on the left side of the cerebellum with a size of 4.44x3.93x4.93 cm, suggesting vestibular schwannoma. The mass also caused the obliteration of the ventricle, causing hydrocephalus.

Conclusion: KWNP is an unusual finding resulting in a paradoxical hemiparesis, a false-localizing neurologic sign. Physicians should recognize KWNP in patients with hemiparesis, especially in space-occupying lesions. Imaging studies can help localize the lesion to minimize misdiagnosis and optimize patient treatment.

Keywords: Cerebellopontine angle, kernohan-woltman notch phenomenon, paradoxical hemiparesis, vestibular schwannoma

Introduction

Expanding intracranial lesions occasionally produces focal neurological signs unrelated to the lesion's location. These paradoxical clinical signs are described as the "false-localizing signs".[1-4] Kernohan-Woltman notch phenomenon is a false-localizing neurologic sign presenting with hemiparesis ipsilateral to the primary lesion.[5] This phenomenon occurs during transtentorial herniation, which causes the contralateral cerebral peduncle to be compressed against the free edge of the tentorium, thus causing compression of descending corticospinal tract fibers.[5-7] Furthermore, the Kernohan-Woltman notch phenomenon is also considered an unusual finding. This article describes a patient with a space-occupying lesion of the cerebellum complaining of ipsilateral hemiparesis. This study aimed to report a vestibular schwannoma in the cerebellopontine angle with paradoxical hemiparesis and the Kernohan-Woltman Notch Phenomenon (KWNP).

Case

A 31-year-old female was presented to the Neurology Clinic of Bhayangkara Hospital TK. I R. Said Sukanto, Jakarta, Indonesia, on 29 November 2021 with a loss of balance since nine months ago. There was no history of trauma or falls. The patient also complained about loss of hearing, vision disturbance, and weakness in the left arm and left leg. Past medical history was unremarkable, and the patient was on no medications. On examination, she was stable hemodynamically,

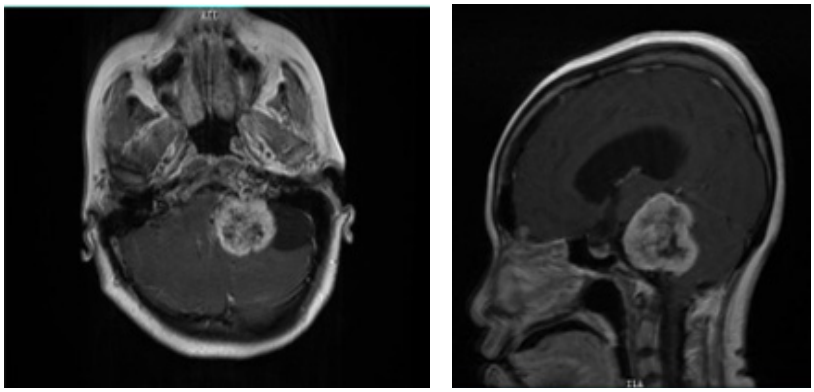

Fig. 1 CPA Mass in Magnetic Resonance Imaging, (A) Axial View, (B) Sagittal View

with reduced left arm and leg muscle strength against resistance (Medical Research Council, MRC, grade 4), deviation of the face to the left, reduced hearing function, and loss of balance. There was also abnormality identified upon finger-to-nose test, dysdiadochokinesia, as well as inability to perform tandem gait. The patient was then admitted for brain magnetic resonance imaging (MRI) which showed a mass in the left cerebellopontine angle (CPA) with a size of 4.44 cm x 3.93 cm x 4.93 cm, suggesting vestibular schwannoma (Fig.1). The mass also caused the fourth ventricle to be obliterated causing hydrocephalus. In this case, the CPA mass could cause the left cerebral peduncle to be compressed, causing a disruption of the descending corticospinal tract. Thus, the patient had a left hemiparesis. The patient did not return to hospital for re-evaluation and surgery.

Discussion

Supratentorial lesions is known as common cause of neurological impairment of movement on the contralateral side of the body, resulting from contralateral corticospinal projections. [7] These projections arise from cortical regions of the brain and decussate in the caudal medulla, then continue traveling down the spinal cord.[8] Almost all fibers decussate, resulting in contralateral clinical findings.[8] However, in a patient following hemorrhage, tumor, abscess, or infarction with brain swelling, a lateral and downward displacement of subthalamic-upper brainstem structures and herniation of the medial part of the temporal lobe into the opening in the tentorium are usually observed in large, destructive or space-occupying lesions. [3] The upper midbrain is pushed against the tentorium's contralateral edge, causing weakness and a Babinski sign ipsilateral to the hemispheral lesion known as the Kernohan-Woltman notch phenomenon (KWNP). [3] KWNP is one of the causes of false localizing neurological signs, manifesting an ipsilateral neurological deficit and defying the corticospinal decussation principles.[9] Kernohan and Woltman propose the mechanism in which the descending pressure caused the squeezing of the cerebral crus's opposite side against the cerebellum's tentorial edge.[10,11] Based on MRI and CT studies by Carrasco *et al*.,[12] direct pressure of the cerebral peduncle from the tentorium would lead to the degeneration of myelinated fibers of the corticospinal tract, which leads to hemiparesis. The corticospinal tract controls voluntary movements for the somatic motor system from the neck to the feet. [13] This tract carries impulses from the primary motor cortex through the internal capsule, cerebral peduncles, and ventral pons, then decussate to the contralateral via the pyramidal decussation.[13]

The false localizing sign of KWNP can cause several diagnostic difficulties in the clinical setting, including operating on the wrong side of the hematoma, requiring neuropsychological testing to localize the lesion, and a case of tetraparesis, leading to a misdiagnosis of consciousness.[4] CPA is a subarachnoid space located in the ventral surface of the brainstem and medial cerebellar hemisphere, bordered laterally by the superior and inferior limbs of the cerebellopontine fissure. Medially at the CPA, the lateral recess of the fourth ventricle opens to the CPA through the foramen of Luschka.[14] Tumors found in this region are usually vestibular schwannoma, also known

as acoustic neuroma, which accounts for 90% of the cases, meningioma (3%), primary cholesteatoma, and facial nerve schwannoma.[15] Tumors in the CPA usually present with signs and symptoms resulting from compression of cranial nerve V, VII, VIII, and lateral aspect of the pons and cerebellar peduncle, which depends on the size and extension of CPA tumors.[15,16] This patient, the findings from an MRI scan suggested a vestibular schwannoma in the left CPA. The patient complained about left-side hemiparesis, right facial palsy, hearing loss, and loss of balance. Surgical approaches for vestibular schwannoma include the retrosigmoid, middle fossa, and translabyrinthine approach.[17] In 208 cases described by Rauniyar *et al*.,[18] the most common complication of patients undergoing the suboccipital retrosigmoid approach was hearing loss (50%), facial nerve palsy (10.09%), and hydrocephalus (8.65%).The middle fossa approach needs to be more utilized compared to the retrosigmoid and translabyrinthine approaches. In an article by Raheja *et al*.,[19] the outcome of 78 patients undergoing the middle fossa approach was generally good, with good functional preservation of the facial nerve (90%), 75.5% with class A/B Association of Otolaryngology-Head and Neck Surgeons (AAO-HNS) hearing class, and no cerebrospinal fluid (CSF) leak, postoperative seizure, and dysphasia. Only three patients reported wound infections. Lastly, the translabyrinthine approach is a practical surgical approach for vestibular schwannoma. In a retrospective study from 1996 to 2017 by de Boer *et al*.,[20] a total of 596 with vestibular schwannoma underwent surgery with a translabyrinthine approach. The facial nerve function is preserved in 509 patients (85%) according to House-Brackmann (HB) grading system with a score of HB 1–2. Postoperative complications that can occur are CPA hematoma, meningitis, CSF leak, and wound infection. De Boer *et al*.[20] also points out that preoperative tumor size is the predictor for postoperative facial palsy.

In conclusion, KWNP is an unusual finding resulting in a paradoxical hemiparesis, a false-localizing neurologic sign. Physicians should be aware of KWNP in a patient with hemiparesis, especially in the setting of space-occupying lesions. Imaging studies can help to localize the lesion to minimize the misdiagnosis and optimize the treatment of the patient.

References

1. Carrasco-Moro R, Castro-Dufourny I, Martínez-San Millán JS, Cabañes-Martínez L, Pascual JM. Ipsilateral hemiparesis: the forgotten history of this paradoxical neurological sign. Neurosurg Focus. 2019;47(3):E7. doi:10.3171/2019.6.FOCUS19337
2. Jang SH, Seo YS. Ipsilateral Hemiparesis Following Epidural Hematoma in a Patient With Traumatic Brain Injury. Ann Rehabil Med. 2019;43(3):352–4. doi:10.5535/arm.2019.43.3.352
3. Ropper AH, Samuels MA, Klein JP, Prasad S. eds. Adams and Victor's Principles of Neurology, 11th ed. McGraw Hill; 2019. p . 386.
4. Zhang CH, DeSouza RM, Kho JS, Vundavalli S, Critchley G. Kernohan-Woltman notch phenomenon: a review article. Br J Neurosurg. 2017 Mar 4;31(2):159–66. doi:10.1080/02688697.2016.1211250
5. Gimarc K, Massagli TL. Kernohan-Woltman notch phenomenon in two patients with subdural hematoma and ipsilateral hemiparesis. Am J Phys Med Rehabil. 2020 1;99(12):1195–6. doi:10.1097/PHM.0000000000001427
6. Ahmed F, Shamim MS, Ali SA. Kernohan–woltman notch phenomenon: case report and review of literature. Pakistan Journal of Neurological Sciences (PJNS). 2017;12(3)44–6.
7. Laaidi A, Hmada S, Naja A, Lakhdar A. Kernohan Woltman notch phenomenon caused by subdural chronic hematoma: Systematic review and an illustrative case. Ann Med Surg (Lond). 2022;79:104006. doi:10.1016/j.amsu.2022.104006
8. Saada F, Antonios N. Existence of Ipsilateral Hemiparesis in Ischemic and Hemorrhagic Stroke: Two Case Reports and Review of the Literature. Eur Neurol. 2014;71(1–2):25–31. doi:10.1159/000356510
9. Simonin A, Levivier M, Nistor S, Diserens K. Kernohan's notch and misdiagnosis of disorders of consciousness. BMJ Case Rep. 2014;2014:bcr2013202094. doi:10.1136/bcr-2013-202094
10. Kernohan JW, Woltman HW. Incisura of the crus due to contralateral brain tumor. Arch Neurol Psychiatry. 1929;21(2):274–87. doi:10.1001/archneurpsyc.1929.02210200030004

11. Lee JH, Kang MR, Kim SJ, Yoo BG, Kim EG, Ji KH. Kernohan-Woltman notch phenomenon caused by a traumatic epidural hematoma. J Neurosonol Neuroimag 2019; 11(2):182–5. https://doi.org/10.31728/jnn.2019.00072
12. Carrasco R, Pascual JM, Navas M, Martínez-Flórez P, Manzanares-Soler R, Sola RG. Kernohan-Woltman notch phenomenon caused by an acute subdural hematoma. J Clin Neurosci. 2009;16(12):1628–31. doi:10.1016/j.jocn.2009.02.015
13. Natali AL, Reddy V, Bordoni B. Neuroanatomy, corticospinal cord tract. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 14, 2023.
14. Tomita T, Grahovac G. Cerebellopontine angle tumors in infants and children. Childs Nerv Syst. 2015;31(10):1739–50. doi:10.1007/s00381-015-2747-x
15. Memari F, Hassannia F, Reza Abtahi SH. Surgical outcomes of cerebellopontine angle tumors in 50 cases. Iran J Otorhinolaryngol. 2015;27(78):29–34.
16. Panigrahi S, Mishra SS, Das S. Primary cerebellopontine angle glioblastoma in an adult. Asian J Neurosurg. 2017;12(1):62–4. doi:10.4103/1793-5482.145323
17. Chamoun R, MacDonald J, Shelton C, Couldwell WT. Surgical approaches for resection of vestibular schwannomas: translabyrinthine, retrosigmoid, and middle fossa approaches. Neurosurg Focus. 2012;33(3):E9. doi:10.3171/2012.6.FOCUS12190
18. Rauniyar S, Gu J, Wang L, Shen Z, Meng Q, Xie S, et al. Cerebellopontine angle tumors: surgical and non-surgical outcomes in a cohort 321 cases. Acta Sci Neurol. 2020;3(6):59–74.
19. Raheja A, Bowers CA, MacDonald JD, Shelton C, Gurgel RK, Brimley C, et al. Middle fossa approach for vestibular schwannoma: good hearing and facial nerve outcomes with low morbidity. World Neurosurg. 2016;92:37–46. doi:10.1016/j.wneu.2016.04.085
20. de Boer NP, Koot RW, Jansen JC, et al. Prognostic factors for the outcome of translabyrinthine surgery for vestibular schwannomas. Otol Neurotol. 2021;42(3):475–82. doi:10.1097/MAO.0000000000002980