ORIGINAL ARTICLE

EFFECT OF EIGHT HOURS PER DAY OF INTERMITTENT SELF-PRONE POSITIONING FOR SEVEN DAYS ON THE SEVERITY OF COVID-19 PNEUMONIA/ ACUTE RESPIRATORY DISTRESS SYNDROME

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Background: Prone positioning improves ventilation-perfusion mismatch, distribution of gravitational gradient in pleural pressure, and oxygen saturation significantly in patients with Covid pneumonia. We aimed to find out the efficacy of eight hours per day of intermittent self-prone positioning for seven days in patients affected with COVID-19 pneumonia/ ARDS. **Methods:** This Randomized Clinical Trial was conducted in the Covid isolation wards of Ayub Teaching Hospital, Abbottabad. Patients suffering from COVID-19 pneumonia/ ARDS were enrolled with permuted block randomization into a control and an experimental group each consisting of 36 patients. Parameters of Pneumonia Severity Index (PSI) score along with other sociodemographic data was noted on a preformed structured questionnaire. Death was confirmed by requesting the death certificate of patients on the 90th day of enrolment. Data Analysis was done with SPSS Version 25. Tests of significance were applied to calculate the difference in the patients of the two groups with respect to respiratory physiology and survival. **Results:** The mean age of the patients was 63.79±15.26 years. A total of 25 (32.9%) male and 47 (61.8%) female patients were enrolled. Statistically significant improvement was found in the respiratory physiology of the patients at 7th and 14th DOA between the groups. Pearson Chi-Square test of significance showed a difference in mortality between the two groups at 14th DOA (*p*-value=0.011) but not at 90th DOA (*p*-value=0.478). Log Rank (Mantel-Cox) test of significance, applied on the Kaplan Meier curve and showed no statistically significant difference among the groups based on the survival of the patients. (*p*-value=0.349). **Conclusion:** Early transient improvement in respiratory physiology and mortality does occur with 8 hours of self-prone positioning for seven days but there is no effect on the 90-day survival of the patients. Thus, the impact of the manoeuvre on improving survival needs to be explored with studies having an application of the manoeuvre for a longer duration and period.

Keywords: COVID-19; Pneumonia; Acute Respiratory Distress Syndrome (ARDS); Prone Positioning; Kaplan Meier Survival Curve

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INTRODUCTION

Coronavirus disease 2019 (Covid-19), a highly contagious viral disease caused by the SARS-CoV-2 virus, involves primarily the respiratory system with the most common symptoms of fever, cough, tiredness, headaches, generalized aches and pains, those with the serious disease may get shortness of breath.[1] Most common complications are Covid pneumonia and acute respiratory distress syndrome.[2] The virus emerged in Hubei province of China where its first case was reported in Dec 2019.[3] The virus spread rapidly around the globe and a pandemic was declared by the WHO on March 11 2020.[3] The index case in Pakistan was reported from Karachi on 26th Feb 2020.[4] As the pandemic peaked, an enormous number of cases with complications such as pneumonia and ARDS aroused requiring much more ICU admissions and invasive ventilations.[2,5] This resulted in overburdening of the health care system, intensive care units and shortage of mechanical ventilators, nearly bringing the healthcare system on verge of collapse even in the developed countries.[6,7] Various other options such as non-invasive ventilation were employed to counter the increasing demand of patients requiring positive pressure ventilation.[5]

Prone positioning has been studied previously and has shown significant results in terms of improving ventilation-perfusion mismatch, distribution of gravitational gradient in pleural pressure, and oxygen saturation.[1,8] Evidence from patients with non-Covid ARDS suggests that gravitational effects and anatomical repositioning relieve the compression effect of heart on the lung parenchyma and improves ventilation from dorsal to ventral areas of lungs.[3,9,10] Similarly early and frequent prone positioning was suggested as evidence supports a decrease in need of intubation and 28-day mortality from 32.8–16% in non-Covid related ARDS.[6,11]

Prone positioning has been adopted as an effective technique to improve the overall outcome of the disease in ARDS around the world. European society of intensive care medicine suggested 12-hour prone positioning in patients with moderate to severe Covid-19 infections.[5] The guidelines of Intensive Care Society (ICS) 2020 state that prone positioning should be applied to all the patients, regardless of the mode of oxygen therapy.[12] Prone positioning manoeuvres have the potential to improve ventilation and can help preserve our limited resources for the benefit of those who are in dire need.[10,13,14]

Therefore, we formulated this study to find out the efficacy of eight hours per day of intermittent self-prone positioning for the first seven days of hospitalization in patients affected with Covid pneumonia/ ARDS in our setup. Results of our study may provide evidence to guide our healthcare staff regarding the management of Covid pneumonia and its complications, i.e., ARDS using this simple and cost-effective technique.

MATERIAL AND METHODS

This Randomized Clinical- open label Trial was conducted from Oct 15, 2021, till February 28, 2022, in the Covid isolation wards of Ayub Teaching Hospital, Abbottabad. Ethical approval was given by the Medical Ethics Committee- Ayub Medical College, Abbottabad, after a thorough assessment of the research proposal (Registration #4916). Clinicaltrial.gov registration number is NTC05405335. Patients with positive COVID-19 PCR or evidence of COVID-19 pneumonia/ARDS on HRCT chest were included in this study after taking written informed consent. Consent was obtained from the first relative and/or the patient where possible. The patients were duly informed of the nature and purpose of the study and their rights to withdraw, once they were conscious and oriented. Consent form was prepared as per WHO guidelines. The consent form was also assessed by the medical ethics committee of Ayub medical college, Abbottabad.

After admission to the covid isolation ward, the patients who had no contra-indications to the prone positioning such as acute bleeding, haemorrhage, shock, raised intracranial pressure, trauma, spinal instability, and pregnant females in the 2nd or 3rd trimester were then enrolled by permuted block randomization into a control and an interventional group. Twelve permuted blocks were made; each consisting of 6 tickets (3 tickets with A and 3 with B on them in each block). After obtaining consent, a ticket was taken from the block by lottery method. A patient who gets a ticket with A on it was put into the experimental group while the patient with B on the ticket was put to control group. Once six patients were selected into the two groups by this method, the process was repeated for the next patient using the next block. A total of 72 patients were included in this study, 36 patients in each group. Data regarding socio-demographic and pneumonia severity index (PSI) scale parameters were collected on a self-developed structured questionnaire from the medical record files of the patients on the 1st, 7th, and 14th day of admission (DOA). Patients who were to be subjected to prone positioning were assisted by experienced staff if the patient requested. The duration of each prone positioning cycle was set for thirty minutes to three hours (duration controlled by the patient) alternating with lying on the right side then on the left side and afterward sitting upright and so on. Total prone positioning duration lasted for eight hours per day for seven days. The duration of each cycle was recorded on the file by the staff. Patients in both groups were visited twice a day (morning at 10:00 am and night at 08:00 pm) by the study team for evaluation and assessment. Physicians and staff of both wards were onboard regarding strict adherence to the hospital protocols for management of patients and the study methodology and protocols were shared with them.

The primary outcome was death within the first seven days of stay in the hospital, the period in which prone positioning was done, and up to 90 days from the day of admission (data was obtained by following the patients through personal contact with the first relative of each patient). Other endpoints were improvement in the respiratory physiology of patients quantified with parameters like PSI score, partial arterial pressure of oxygen (PaO2), type of mask for supplemental oxygen therapy, and respiratory rate (RR). Data regarding the socio-demographic and PSI parameters of the patients were collected at the time of enrolment into the study just after randomization. Clinical parameters were noted down after putting the patients in a supine position for at least ten minutes.

Data were analyzed using SPSS version 25. Normally distributed data were presented as mean and standard deviation (SD), while non-normally distributed data were presented as median and range. The baseline characteristics at 1st DOA and the changes in our observed parameters at 7th and 14th DOA were tested for significant difference between the groups via an independent samples t-test for normally distributed variables and independent samples Mann-Whitney U-test/ Kruskal-Wallis test, as appropriate, for non-normally distributed variables. Correlation between the continuous variables was assessed by utilizing the spearman's rho test. Survival analysis was done according to the Kaplan-Meier method and the results for the two groups were compared for significance via the Log-rank test. A *p*-value of 0.05 was considered statistically significant.

RESULTS

The data for partial arterial pressure of oxygen at the 1st, 7th, and 14th day of admission (DOA) and age were found normally distributed whereas the rest of our study parameters showed a significant departure from normality on the Shapiro-Wilk test. The mean age of the patients was 63.79±15.26 years. Table 1 shows the socio-demographic parameters of participants from both groups of our study.

Table-2 shows the mean and standard deviation (SD) for Partial arterial pressure of oxygen (PaO2) values which were measured on arterial blood gases automatic analyzer and the mean respiratory rate (RR) on the 1st, 7th, and 14th day of admission (DOA) separately for the patients of both groups.

An independent sample t-test was applied to see if there is any significant difference between the control and experimental groups concerning the PaO2 and respiratory rate (RR) at the 1st, 7th, and 14th DOA. As shown in table 2, a significant difference was found in the mean partial pressure of oxygen in the arterial blood at the 7th and 14th DOA between the control and experimental groups. Also, a statistically significant decrease in the respiratory rate was observed at the 14th DOA. This increase in the oxygen partial pressure in the arterial blood and the decrease in dyspnoea indicates improved oxygenation/ ventilation of the patients who were subjected to prone positioning.

Table-3 shows the mask types. These are simple mask (which delivers up to 8 l/min oxygen), non-re-breathable mask (NRM) (which delivers up to 15 l/min oxygen), and the non-invasive ventilation (NIV), i.e., CPAP which delivers up to 15l/min oxygen with high-end expiratory pressure. As evident from table-3, the oxygen requirement of the patients in the experimental group decreased with time and more patients are put on the simple masks.

Independent samples Mann-Whitney U test and independent-sample Kruskal-Wallis test for non-normally distributed data were applied where appropriate, on the median PSI scores at 1st, 7th, and 14th DOA and given groups to check any significant difference among these parameters across these groups. The results are shown in Table-4, where a significant difference was found in the mean PSI scores at the 7th and 14th DOA between control and experimental groups, representing a statistically significant gradual decrease in the severity of disease in the prone positioned patients group as compared to the no significant difference in the severity of disease at the time of enrolment among the patients of the two groups. There is no statistically significant difference in the severity of disease among the hypertensive and non-hypertensive patient groups at no point in time. On the other hand, the diabetic patients had significantly higher values of PSI scores and hence more severe disease at all times. The PSI score values of the patients who died during the study period were significantly higher right at all the observation times. This indicates that a higher PSI score is associated with a higher mortality rate.

The distribution of the PSI score at the 1st, 7th, and 14th DOA of the fully vaccinated, partially vaccinated and non-vaccinated patient's groups showed a *p*-value of 0.452, 0.384, and 0.209 respectively, proving no statistical difference in the PSI scores of the patients from among the two groups at the specified days. These findings may not apply to the general population as only patients with pneumonia were enrolled in this study. To draw such conclusions, a population-based study with a huge sample size is required.

Spearman's rho test was performed to examine the relationship between the age of the patients and the PSI scores at 1st, 7th, and 14th DOA respectively and the results are shown in Table-5. The PSI score was positively related to the age of the patients at 1st, 7th, and 14th DOA with a level of 0.01 (2-tailed). This indicates that with the increasing age of the patients, there is a greater chance of having a higher PSI score from covid pneumonia and hence a more severe disease.

A 2x2 cross-tabulation of patient stats and group at 14th and 90th DOA is shown in table 6. Only 2 patients died in the experimental group during the first 14 days, and 18 patients died till the last day of follow up while 10 patients died during the first 14 days in the control group and a total of 21 died till the 90th day. The resulting mortality calculated from it is shown in figure-1. Kaplan Meier survival analysis was done to compare the means and medians of the survival time (taken in days) for the control and experimental groups. The Kaplan Meier survival curve was derived through the SPSS version 25, for the visual comparison of the two groups- Figure-2. As seen in figure-2, the experimental group's survival is better than the control group right after the third to the fourth day of admission. The difference in survival is more evident up to the first twenty-five days but then this gap in survival reduces. Log Rank (Mantel-Cox) test of significance was applied to see if the difference in the survival time between the two groups was statistically significant. A *p*-value of 0.349 was obtained showing that there is no statistically significant difference between the two groups based on the survival of the patients from the two groups.

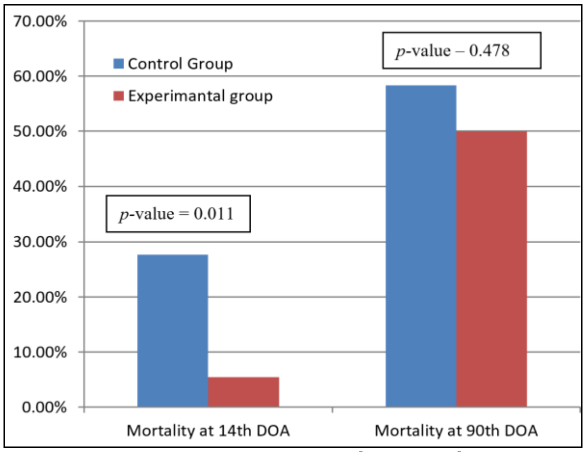

Figure-1: Mortality at 14th and 90th DOA

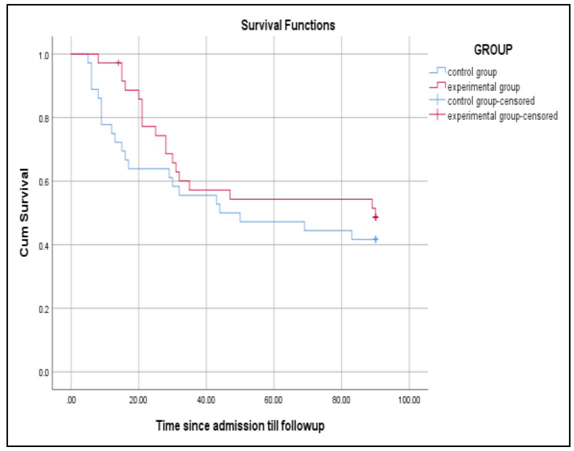

Figure-2: Kaplan Meier Survival Curve

Table-1: Sociodemographic parameters of patients

Parameters	Categories	Control group	Experimental group	Total
Gender	Male	12	13	25 (32.9%)
	Female	24	23	47 (61.8%)
HTN	Non-hypertensive	18	14	32 (42.1%)
	Hypertensive	18	22	40 (52.6%)
DM	Non-diabetic	20	24	44 (57.8%)
	Diabetic	16	12	28 (36.8%)
Vaccination	First dose received	14	2	16 (21.05%)
	Not vaccinated	22	28	50 (65.78%)

Table-2: Mean PaO_2 and Respiratory Rate (RR) of patients

Parameter	Mean of control group	Mean of experimental group	*p*-value
PaO_2 at 1st DOA	61.46±15.69	67.64±16.45	0.108
PaO_2 at 7th DOA	63.51±15.49	74.15±11.91	0.004
PaO_2 at 14th DOA	63.28±17.40	81.12±12.11	0.000
RR at 1st DOA	25.64±5.27	27.0278±3.73773	0.201
RR at 7th DOA	24.03±5.25	23.9444±3.63274	0.935
RR at 14th DOA	25.53±4.79	20.6857±3.32346	0.002

Table-3: Mask type used for oxygen supplementation

Group	Mask type			
	Simple mask	NRM	NIV	Total
Control group (1st DOA)	10	26	0	36
Experimental group (1st DOA)	14	19	3	36
Control group (7th DOA)	7	15	7	29
Experimental group (7th DOA)	15	17	4	36
Control group (14th DOA)	6	6	3	15
Experimental group (14th DOA)	18	13	4	35

Table-4: Cross tabulation of median PSI score at 1st, 7th and 14th DOA x Group

Group		PSIscore00	PSIscore07	PSIscore14
Control group	Median	100.0000	91.0000	90.0000
	N	36	29	14
Experimental group	Median	94.3333	84.5000	77.1429
	N	36	36	35
Mann-Whitney’s U test P Value		0.307	0.037	0.026
Male	Median	105.0000	90.0000	81.6667
	N	25	20	16
Female	Median	94.2500	85.0000	81.3333
	N	47	45	33
Mann-Whitney’s U test P Value		0.029	0.176	0.873
Non-Hypertensive	Median	94.6000	84.0000	74.0000
	N	32	27	20
Hypertensive	Median	100.7500	89.2500	82.0000
	N	40	38	29
Mann-Whitney’s U test P Value		0.149	0.085	0.318
Non-diabetic	Median	92.5000	84.0000	75.0000
	N	44	39	29
Diabetic	Median	107.5000	96.5000	88.0000
	N	28	26	20
Mann-Whitney’s U test P Value		0.005	0.006	0.012
Alive	Median	90.1429	81.3333	72.0000
	N	33	30	22
Dead	Median	106.0000	90.6667	85.0000
	N	39	35	27
Mann-Whitney’s U test P Value		0.000	0.002	0.006
Not Vaccinated	Median	94.5000	85.0000	80.0000
	N	50	46	35
Partially Vaccinated	Median	109.0000	90.0000	85.0000
	N	11	9	7
Fully Vaccinated	Median	100.0000	91.5000	140.0000
	N	5	4	1
Kruskal-Wallis Test (P Value)		0.452	0.384	0.209

Table-5: Spearman's correlation between age of patients and PSI score

		PSIscore00	PSIscore07	PSIscore14
AGE	Spearman’s rho	.361**	.557**	.515**
	Sig. (2-tailed)	.002	.000	.000
	N	72	65	49
**. Correlation is significant at the 0.01 level (2-tailed).				

Table-6: Cross tabulation between the groups and status at 14th and 90th day of enrollment

Status at 14th DOA	Dead	Alive	Total
Control group	10	26	36
Experimental group	2	34	36
Total	12	60	72
Status at 90th DOA			
Control group	21	15	36
Experimental group	18	18	36
Total	39	33	72

DISCUSSION

In this randomized clinical trial, a controlled assessment of 72 patients suffering from Covid-19 pneumonia/ ARDS was done to establish the efficacy of prone positioning. The effects of prone positioning on survival, blood respiratory physiology, and mortality rate on the 14th and 90th day of admission were done for the control and experimental groups each consisting of 36 patients.

The majority of the participants in our study were females (61.8%). This is contrary to the published literature where a majority of the studied population is male. Most of those studies are either observational cohort studies or reviews and meta-analyses of such studies and case reports.[5,6] The mean age of the patients was 63.79±15.26 years. It correlates with the published literature where the mean age of the patients is around 60 years.[3,6] Only 21.05% of them had received a single dose of vaccination for Covid 19.

The percentage of antihypertensive patients was 52.6% while only 36.8% were diabetic.

In this study, the mean PaO2 for control and experiment groups at 1st DOA showed no statistically significant difference on t-test analysis (*p*-value=0.108). After the application of the prone positioning manoeuvre on the patients of the experimental group, the mean PaO2 showed a significant increase at the *p*-value of 0.004 and 0.000 for the 7th and 14th DOA respectively. We also found a significant decrease in the respiratory rate at 14th DOA in the patients of the experimental group (*p*-value=0.002) and an increasing trend of patients being put on a simple mask from NRM/CPAP indicating lesser oxygen supplementation requirement. This shows a beneficial effect of prone positioning on respiratory physiology. This beneficial effect could be since prone positioning improves ventilation, thus improving oxygenation of blood which may reduce the excessive work of breathing on the muscles of respiration, reducing their fatigue; preventing the patient from the need for CPAP/Intubation and the subsequent barotrauma caused to the lungs.[15] This result of our study is consistent with Weatherald J *et al*, in their rapid review of uncontrolled cohort studies, described an improvement in oxygenation of patients stating that it's beneficial only in cases of moderate to severe ARDS.[16]

Solverson K *et al* Researchers reported improvement of mean PaO2 from 91% in the supine position to 98% in the prone position and a decrease in respiratory rate from 28 to 22 breaths per minute – study done in Canada.[3] Wendt *et al*. conducted their study in Morristown New Jersey and reported that the median SpO2 rose from 83% without oxygen to median SpO2 of 96% with oxygen and prone positioning and a decrease of respiratory rate from 31±9 breaths per minute to 26±8 breaths per minutes.[11] Altinay M *et al*. from Istanbul- Turkey reported median SpO2 of prone positioned group 95% and median PaO2 82% whereas for the non-prone positioned group of patients median SpO2 was 90% and PaO2 was 66 mmHg.[17] Therefore, researchers regarded it as a promising therapy for acute hypoxemic respiratory failure as it demonstrated effectiveness by causing improvement of respiratory physiology of the patient's with moderate acute hypoxemic respiratory failure.[15,16,18] Researchers have declared prone positioning manoeuvre as an economical and easy early/ emergency intervention in such cases.[16,18,19] Another review article although observed an improvement of oxygenation and dyspnoea with the use of prone position manoeuvre in patients with hypoxemic respiratory failure secondary to covid 19 related lung injury, also concluded that currently no evidence has been found to suggest if prone positioning will either delay or avoid the need for CPAP/ Intubation or who will benefit more from the intervention.[20]

The PSI score indicates the severity of the disease, i.e., the higher the value of the PSI score, the more severely affected the lungs of the patient are. We compared the PSI score median values for the control and experimental group at 1st, 7th, and 14th DOA. The Mann-Whitney's U test suggested that the difference in the PSI score values was not significant (*p*-value=0.307) between the two groups at the start of the trial but later on, a statistically significant decreasing trend has been noted in the PSI scores of the experimental group with *p*-values of 0.037 and 0.026 noted at 7th and 14th DOA respectively. Similarly, the independent samples Mann-Whitney's U test results showed significantly higher initial PSI score values for the male gender but later the difference disappeared. Similarly, the diabetic and hypertensive patients had significantly higher PSI scores throughout as well as the patients who died during the study observation period. A study reported significantly increased mortality of patients suffering from covid disease having comorbidities such as hypertension, diabetes, obesity, cardiovascular diseases, cancer, and age above 65 years.[21]

Spearman's rho test showed a positive correlation between the increasing age and the severity of the disease. These results show that the covid 19 infection is more virulent for the patients who had a weak immune system due to any chronic disease such as hypertension and diabetes or an upper extreme of age, as no patient of lower extreme of age was enrolled in the study. Also, it suggests that those patients who are more severely affected at the presentation to a clinician are more likely to die of covid pneumonia and ARDS. A meta-analysis on mortality of covid also found a significant association between increasing age and covid disease-related mortality.[21] A retrospective observational study also discussed Gender, comorbidity state, and BMI but reported no statistically significant effect of the mentioned parameters on the severity of the disease. The study lacks discussion of these parameters on the severity of the disease and the effects of prone positioning simultaneously.[11]

A comparison of the mortality of the patients on the 14th and 90th day indicated a statistically significant difference in the mortality of the patients among the two groups at the 14th DOA but the difference in mortality becomes insignificant at 90th DOA. It indicates a transient beneficial effect of prone positioning on survival. This transient difference in mortality may be due to the transient beneficial effects of prone positioning which improves oxygenation of blood. Researchers have shared this short-term lower mortality rates in the prone positioned groups but the effect was only transient.[11] Another meta-analysis of non-randomized trials also reported a transient lower incidence of mortality in the prone positioned patients.[6] A systematic review of proportional outcomes comparing observational studies with and without prone positioning in the settings of covid 19 pneumonia demonstrated improved mortality but the difference was not statistically significant.[22]

The Kaplan-Meier curve of survival shows that patients in the experimental group have a transient better survival than the control group right after the third to the fourth day of admission. The difference in survival is more evident up to the first twenty-five days but then this gap in survival reduces. Log Rank (Mantel-Cox) test of significance showed no statistically significant difference between the two groups based on the survival of the patients. a randomized clinical meta-trial conducted in five different regions of the world with a median duration of prone positioning of patients for 5 hours concluded that there was no statistically significant difference in the 28-day mortality between the two groups on Kaplan-Meier analysis.[23] Another retrospective multicenter observational cohort study also published no beneficial effects of prone positioning on the 30-day survival difference as estimated by utilizing Kaplan-Meier analysis.[5]

CONCLUSION

Intermittent prone positioning for 8 hours per day for seven days at the patient's ease is a useful, cost-effective, and emergency intervention that can be easily done to improve the patient's respiratory physiology transiently, helping to stabilize the worsening blood levels of oxygen in any emergency considering the contraindications as well. However, we could not deduce from our data a significant improvement in survival with the use of this manoeuvre. Further research might prove a long-term beneficial effect if the prone positioning manoeuvre is done for patients either a longer duration per day and/ or more than one-week period, possibly months or until certain cut-off values of respiratory physiology parameters are reached.

Our limitations include small sample size, single-center, and demographics; therefore, this study may have limited generalizability.

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AUTHORS' CONTRIBUTION

HJ, FQ, MNAK: Conceptualization of the study design, data collection, analysis, literature search, write-up, proof reading. MA, AE, HH: Data collection, write-up, proof reading. SK, SQM, KA: Literature search, data analysis and interpretation, proof reading.

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