



ORIGINAL: Comparison of Pulmonary Function Tests in Patients with Sick Cell Anemia and Sick Beta-Thalassemia Referring to the Hematology Clinic of Bandar Abbas Shahid Mohammadi Hospital with the Control Group in 2019-2020

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ABSTRACT

Introduction: Due to the high prevalence of sickle cell anemia and beta-shaped sickle cell thalassemia in this region, we decided to conduct this study with the aim of investigating the status of pulmonary function in these patients in Bandar Abbas.

Material and Methods: The statistical population in this study included all patients with sickle cell anemia and sickle cell beta-thalassemia who had referred to the hematology clinic from 2019-2020, which was equal to 60 people. Also, the workers who had referred to the specialized lung clinic for periodic health tests entered the study by observing the criteria for leaving the review as a control group. Demographic information in both groups was collected in a pre-prepared checklist. Then Participants were subjected to spirometry and pulmonary volumes were measured.

Results: The patients in the case group, 39 (65%) were from sickle cell anemia, and 21 (35%) were from the sickle cell beta-thalassemia. In this study, all the studied parameters had a significant difference between the study group and the control, except for the mean age ($p=0.906$). In the control group, the values of FEV1 (Forced expiratory volume in 1 second), FVC (Forced vital capacity), and FEF25-75% (Forced expiratory flow 25-75%) are higher than these values in the case group, and this difference is significant ($P < 0.001$).

Conclusion: The results of the present study showed that the levels of FEV1, FVC and FEF 25-75% in the control group are higher than these values in the patient group and this difference is significant.

Introduction

Sickle cell is one of the most common hemoglobinopathies in which point mutation in beta-globin gene leads to the displacement of valin instead of glutamic acid at the site of the sixth amino acid and

causes hemoglobin S. Complications and symptoms of sickle cell include hemolytic anemia and small vascular obstruction, which can cause acute, chronic or ischemic pain (2), hemolysis can cause chronic anemia and

gallbladder pygma (3). Vascular obstruction causes recurrence of episodic pain as well as complications of damage to organs such as lung, kidney, liver and heart that cause disability and death in patients (4) acute pain periods, which are the most common vascular obstructive accident in patients with sickle cell and a large number of patients encountered during their disease, is called crisis sickle cell. Sickle cell can be heterozygote (sickle cell trait), which is a completely benign state and often has none of the symptoms and symptoms of sickle cell anemia. Sickle cell can be used with other hemoglobinopathies such as beta-thalassemia, hemoglobin C, E, D. Cases where sickle cell is associated with beta thalassemia is known as sickle cell thalassemia (1). One of the most important complications of sickle cell is pulmonary problems in patients that leading to abundant morbidity and mortality (6). Pulmonary problems in these patients can include chronic shortness of breath to Acute Chest Syn, changes in pulmonary function, asthma or frequent wising without diagnosis of asthma, increased pulmonary hypertension, chronic or acute venous thromboembolic disease, pulmonary fibrosis, sleep respiratory disorders. Lung function is not normal in most patients with sickle cell disease (7, 8). Considering that the studies on pulmonary function changes in these patients are low and especially in our country Iran has not been done and there is a difference in the pattern of changes in pulmonary function tests with other countries, and also considering the importance of the subject and the significant effect of pulmonary function disorders on morbidity and mortality in patients with sickle cell anemia and beta-thalassemia sickle, we aimed to investigate the pulmonary function status of patients with sickle cell and β -thalassemia/ sickle cell in Bandar Abbas according to the prevalence of this disease.

Methods

This case-control study was conducted during 2018-2019 with the aim of comparing

pulmonary function tests in patients with sickle cell anemia and beta-thalassemia/ sickle cell referred to hematology clinic of Shahid Mohammadi Hospital in Bandar Abbas. The target population consisted of all patients with sickle cell anemia and beta-thalassemia who had referred from January 2018 to January 2019. According to previous studies, the standard deviation of FEV1 was 11.6, considering error of 5%, test power 80% and effect size 6, sample size was determined 60 for each case and control group using formula;

$$n=2(Z1-\alpha/2+Z1-\beta)^2 \gamma^2 d^2 / \epsilon^2$$

The sampling method was easily available. This study was conducted after obtaining the necessary permissions and receiving the code of ethics. From all patients with anemia referred to hematology clinic of Shahid Mohammadi Hospital in Bandar Abbas by internal resident and hematology specialist, history was obtained and after electrophoresis of serum hemoglobins, diagnosis of sickle cell anemia and beta-thalassemia/ sickle was determined, and then according to exclusion criteria, these subjects underwent spirometry as case group. The workers who were not smokers and had no history of previous pulmonary disease and cortone use and referred to subspecialty pulmonary clinic for periodic health tests and had no anemia in blood cell count test (hemoglobin more than 13 in men and more than 12 in women) as control group underwent spirometry with the above mentioned device. Parameters such as FEV1 (exhaust air volume in the first second of forced exhalation), FVC (compulsory and high-pressure vital capacity), FEV1/FVC (fraction of the vital output capacity in the first second of exhalation), FEF25-75% (average airflow during the time period of 25-75% of lung volume has been emptied). Both groups were recorded and collected in a checklist. Inclusion criteria are patients with anemia referred to Shahid Mohammadi Hospital in Bandar Abbas who were diagnosed with tuberculosis anemia and β -thalassemia/sickle in serum electrophoresis

and had informed consent for spirometry. Exclusion criteria were: Crisis sickle cell, previous lung disease, Smoker, history of oral corton consumption during the past 8 weeks, history of inhaled corton consumption during the past 4 weeks, dissatisfaction with spirometry. Finally, data were compared and analyzed in both case and control groups and Kolmogorov-Smirnov test was used to investigate the distribution of quantitative data in the groups, and in case of normal distribution in each group, independent t-test and otherwise Mann-Whitney test were used. Chi-square test was used to investigate the qualitative variables. The cost of spirometry, its importance and role in health promotion were explained to the subjects and after obtaining consent, they underwent pulmonary

function tests by MIR spirometry model TUK-MIR009.

Results

A total of 60 anemia patients referred to hematology clinic of The Prophet Azam Complex in Bandar Abbas (case group) and 60 patients referred to subspecialty pulmonary clinic for periodic health tests (control group) were evaluated according to the inclusion and exclusion criteria of the study. Among the patients in the case group, 39 (65%) were sickle cell anemia and 21 (35%) were β -thalassemia/sickle. Quantitative data distribution in groups was investigated by Kolmogorov-Smirnov test (*Table 1*). If the data distribution was normal in each group,

Table 1. Distribution of quantitative variables by two groups according to kolmogorov-smirnov test

Groups		Case		Control		
Variables	Test Statistics	P-value	Normality	Test Statistics	P-value	Normality
Age	0.172	<0.001	No	0.137	0.007	No
Length	0.080	0.200	Yes	0.078	0.200	Yes
Weight	0.094	0.200	Yes	0.066	0.200	Yes
BMI	0.198	<0.001	No	0.83	0.200	Yes
Hb	0.222	<0.001	No	0.68	0.200	Yes
MCV	0.205	<0.001	No	0.098	0.200	Yes
MCH	0.438	<0.001	No	0.142	0.004	No
FEV1	0.079	0.200	Yes	0.074	0.200	Yes
FVC	0.104	0.169	Yes	0.078	0.200	Yes
FEV1/FVC	0.061	0.200	Yes	0.047	0.200	Yes
FEF 25%-75%	0.071	0.200	Yes	0.065	0.200	Yes

independent t-test and otherwise Mann-Whitney test were used. Chi-square test was used to investigate the qualitative variables. Demographic data based on the results of *Table 2* showed that the mean age in the control group was 27.6 ± 42.69 years and in the case group was 27.47 ± 47.27 years, which according to Mann-Whitney test, there was no significant difference between the two

groups in terms of age ($P=0.906$). The mean height of the subjects in the control group was 170.75 ± 75 cm and in the case group was 164.55 ± 28 cm, which according to the independent t-test, there was a significant difference between the two groups in terms of height ($P<0.001$). The mean weight of the subjects in the control group was 16 ± 23.77 kg and in the case group was 54.22 ± 24.24 kg,

Table 2. Mean, standard deviation of contextual quantitative variables in the subjects divided into two groups

Groups		Case		Control		P-value
Variables	Mean	SD	Mean	SD		
Age	27.47	8.27	27.42	6.69	0.906	
Length	164.55	8.28	170.75	8.09	<0.001	
Weight	54.22	9.24	77.23	16.17	<0.001	
BMI	19.83	3.37	26.50	4.68	<0.001	
Hb	9.51	1.10	13.00	0.43	<0.001	
MCV	79.23	9.60	86.34	2.02	<0.001	
MCH	26.53	4.40	29.12	7.78	0.011	

Table 3. Mean, standard deviation of pulmonary function tests in the subjects were divided into two groups.

Groups Variables	Case		Control		P-value
	Mean	SD	Mean	SD	
FEV1	70.70	16.78	90.35	11.06	<0.001
FVC	73.43	16.64	89.98	11.14	<0.001
FEV1/FVC	83.05	7.05	81.79	1.96	0.187
FEF25-75%	59.97	19.09	86.13	19.54	<0.001

which according to the independent t-test, there was a significant difference between the two groups in terms of weight ($P<0.001$) The mean BMI was 26.50 ± 4.68 in the control group and $19.83\pm3\pm37$ in the case group, which according to Mann-Whitney test, there was a significant difference between the two groups in terms of BMI ($P<0.001$). The mean Hb of the subjects in the control group was 13.00 ± 0.43 and in the case group was 9.51 ± 1.10 , which according to Mann-Whitney test, there was a significant difference between the two groups in terms of Hb ($P<0.001$).

Comparison of pulmonary function tests between case and control groups

Demographic data showed that 28.3% of the subjects (17 persons) in the control group and 48.3% of the subjects (29 persons) in the case group were women, which according to chi-square test, there was no significant difference between the two groups in terms of gender ($P<0.001$) of the subjects (12 persons) were in the control group and 78.3% (47 persons) in the case group were less than or equal to 30 years old. According to the results of [table 3](#), the mean percentage of FEV1 (Forced expiratory volume in 1 second) in the control group was $90.35\pm11.06\%$ and in the case group was $70.70\pm16.78\%$, according to the results of [table 3](#). Independent t-test

showed a significant difference between the two groups in terms of FEV1 ($P<0.001$). There was a significant difference between the two groups in terms of FVC ($P<0.001$). The mean FEV1/FVC ratio in the control group was 81.79 ± 1.96 and in the case group was 83.05 ± 05.05 , which according to independent t-test, there was no significant difference between the two groups in terms of FEV1/FVC ($P=0.187$). According to independent t-test, Mean of FEF25-75% (Forced expiratory flow 25-75%) In the control group, $86.13\pm19.54\%$ and in the patients group 59.97 ± 19.09 ($P<0.001$).

Comparison of pulmonary function tests between case and control groups by sex groups

According to [table 4](#) results, the mean percentage of FEV1 in the control group was $93.24\pm11.01\%$ and in the case group was $72.17\pm00\pm00\%$, which according to independent t-test, there was a significant difference between the two groups in terms of FEV1 ($P<0.001$). The mean percentage of FVC in the control group was $91.88\pm13.19\%$ and $76.34\pm34\pm52\%$ in the case group, which according to independent t-test, there was a significant difference between the two groups in terms of FVC ($P=0.004$). The mean FEV1/FVC ratio in the control group was 82.19 ± 19.78 and in the case

Table 4. Mean, standard deviation of pulmonary function tests of the subjects in the two groups by sex

Sex	Groups	Case		Control		P-value
	Functional lung test	Mean	SD	Mean	SD	
Female	FEV1	72.00	17.80	93.24	11.10	<0.001
	FVC	76.34	18.52	91.88	13.19	0.004
	FEV1/FVC	82.28	6.49	82.19	0.78	0.943
	FEF25-75%	58.45	16.80	93.00	22.84	<0.001
Male	FEV1	69.48	15.97	89.21	10.97	<0.001
	FVC	70.71	14.44	89.23	10.30	<0.001
	FEV1/FVC	83.77	7.57	81.63	2.25	0.137
	FEF25-75%	61.39	21.20	83.42	17.63	<0.001

group was 82.28 ± 28.49 , which according to independent t-test, there was no significant difference between the two groups in terms of FEV1/FVC ($P=0.943$). The mean fef25-75% percentage in the control group was $93.00 \pm 22.84\%$ and in the case group was $58.45 \pm 16.80\%$, which according to independent t-test, there was a significant difference between the two groups in terms of FEF25-75% ($P<0.001$). According to [table 4](#) results, the mean percentage of FEV1 in the control group was $89.21 \pm 10.97\%$ and in the case group was $69.48 \pm 15.97\%$, which according to independent t-test, there was a significant difference between the two groups in terms of FEV1 ($P<0.001$). The mean percentage of FVC in the control group was $89.23 \pm 10.30\%$ and in the case group was $70.71 \pm 14.44\%$, which according to independent t-test, there was a significant difference between the two groups in terms of FVC ($P<0.001$). The mean FEV1/FVC ratio in the control group was 81.63 ± 25 and in the case group was 83.77 ± 77.57 , which according to independent t-test, there was no significant difference between the two groups in terms of FEV1/FVC ($P=0.137$). The mean FEF25-75% percentage in the control group was $83.17 \pm 42.63\%$ and in the case group was $61.39 \pm 20\%$, which according to independent t-test, there was a significant difference between the two groups in terms of FEF25-75% ($P<0.001$).

Comparison of mean pulmonary function tests between case and control groups by age groups

According to [table 5](#) results, in people less

than or equal to 30 years old, the mean FEV1 percentage in the control group was $87.11 \pm 83.32\%$ and in the case group was $70.94 \pm 16.68\%$, which according to independent t-test, there was a significant difference between the two groups in terms of FEV1 ($P=0.002$). The mean FVC percentage in the control group was $90.50 \pm 12.67\%$ and $73.16 \pm 34.50\%$ in the case group, which according to independent t-test, there was a significant difference between the two groups in terms of FVC ($P=0.001$). The mean FEV1/FVC ratio was 82.07 ± 0.74 in the control group and 83.58 ± 58.40 in the case group, which according to independent t-test, there was no significant difference between the two groups in terms of FEV1/FVC ($P=0.943$). The mean fef25-75% percentage was $75.92 \pm 16.70\%$ in the control group and $61.43 \pm 20 \pm 09\%$ in the case group, which according to the independent t-test, there was a significant difference between the two groups in terms of FEF25-75% ($P=0.025$).

According to the results of [Table 5](#), in people over 30 years of age, the mean percentage of FEV1 in the control group was $90.98 \pm 11.03\%$ and in the case group was $69.85 \pm 17.81\%$, which according to independent t-test, there was a significant difference between the two groups in terms of FEV1 ($P=0.001$). The mean percentage of FVC in the control group was $89.85 \pm 10.87\%$ and in the case group was $73.77 \pm 17.81\%$, which according to independent t-test, there was a significant difference between the two groups in terms of FVC ($P=0.008$). The mean FEV1/FVC ratio was 81.72 ± 2.16 in the control group and

Table 5. Mean, standard deviation of pulmonary function tests of the subjects in the two groups by age group

Age	Groups	Case		Control		P-value
	Functional lung test	Mean	SD	Mean	SD	
≤30	FEV1	70.94	16.68	87.83	11.32	0.002
	FVC	73.34	16.50	90.50	12.67	0.001
	FEV1/FVC	83.58	7.40	82.07	0.74	0.943
	FEF25-75%	61.43	20.09	75.92	16.70	0.025
>30	FEV1	69.85	17.81	90.98	11.03	0.001
	FVC	73.77	17.81	89.85	10.87	0.008
	FEV1/FVC	81.15	5.44	81.72	2.16	0.715
	FEF25-75%	54.69	14.38	88.69	19.51	<0.001

Table 6. Mean, standard deviation of pulmonary function tests of case group in two sex groups

Sex	Male		Female		P-value
Functional lung test	Mean	SD	Mean	SD	
FEV1	69.48	15.97	72.00	17.80	0.566
FVC	70.71	14.44	76.34	18.52	0.192
FEV1/FVC	83.77	7.57	82.28	6.49	0.415
FEF25-75%	61.39	21.20	58.45	16.80	0.556

81.15±5.44 in the case group, which according to independent t-test, there was no significant difference between the two groups in terms of FEV1/FVC (P=0.715). The mean fef25-75% percentage in the control group was 88.19±69.51% and in the case group was 54.69±14.38%, which according to the independent t-test, there was a significant difference between the two groups in terms of FEF25-75% (P<0.001).

Comparison of mean pulmonary function tests of two sex groups in the case group

According to *table 6* results, the mean percentage of FEV1 in women was 72.11±17.80% and in men was 69.48±15.97%, which according to independent t-test, there was no significant difference between the two groups in terms of FEV1 (P=0.566). The mean percentage of FVC was 76.34±18.52% in women and 70.71±14.44% in men, which according to independent t-test, there was no significant difference between the two groups in terms of FVC (P=0.192). The mean FEV1/FVC ratio was 82.28±6.49 in women and 83.77±7.57 in men, which according to independent t-test, there was no significant difference between the two groups in terms of FEV1/FVC (P=0.415). The mean fef25-75% percentage in women was 58.45±16.80% and 61.21±39.20% in men and 75-75% in terms of FEF25 according to independent

t-test (P=0.556).

Comparison of mean pulmonary function tests of two age groups in the case group

According to the results of *Table 7*, in the case group, the mean percentage of FEV1 in the group of people less than or equal to 30 years was 70.16±94.68% and in the group of people over 30 years was 69.85±17.81%, which according to independent t-test, there was no significant difference between the two groups in terms of FEV1 (P=0.838). The mean percentage of FVC in the group of people less than or equal to 30 years was 73.34±16.50% and in the group of people over 30 years was 73.77±17.81%, which according to independent t-test, there was no significant difference between the two groups in terms of FVC (P=0.935). The mean FEV1/FVC ratio was 83.58±7.40 years in the group less than or equal to 30 years and 81.15±5.44 in the group of subjects over 30 years, which according to independent t-test, there was no significant difference between the two groups in terms of FEV1/FVC (P=0.275). The mean fef25-75% percentage in the group of people less than or equal to 30 years was 61.43±20.09% and in the group of people over 30 years was 54.14±69.38%, which according to independent t-test, there was no significant difference between the two groups in terms of FEF25-75% (P=0.264).

Table 7. Mean, standard deviation of pulmonary function tests of case group in two age groups

Age	>30		≤30		P-value
Functional lung test	Mean	SD	Mean	SD	
FEV1	69.85	17.81	70.94	16.68	0.838
FVC	73.77	17.81	73.34	16.50	0.935
FEV1/FVC	81.15	5.44	83.58	7.40	0.275
FEF25-75%	54.69	14.38	61.43	20.09	0.264

Discussion

In many cases, acute and chronic pulmonary complications occur in SCD patients and cause most SCD-related deaths in adults. Although the pathogenesis of chronic pulmonary disease in SCD is not clearly defined, the recurrent occlusion of small vessels causes endothelial dysfunction and loss of lung parenchymal tissue and ultimately lung dysfunction (12-9). Since the severity of complications in different types of sickle cell anemia may be different, in this study we investigated the pulmonary function of these patients. Demographic data in this study showed that there was no significant difference between the case and control groups and the rest of the studied parameters had significant differences between the case and control groups. In study R. Purohit et al., (13) who were used to determine pulmonary function abnormalities in children with sickle cell disease (SCD) showed that pulmonary function in children with SCD compared to the control group was that FEV1 and FVC was lower in the patient group than the control group ($P=0.001$), but the FEV1/FVC ratio was higher in the patients than the control group, but it was not statistically significant ($P=0.06$). Also, in the study of Achigbu et al., (14) in pulmonary function of children with sickle cell anemia compared to the control group, it was shown that children with Sickle Cell Anemia (SCA) had lower levels of FEV1, FVC and PEFR compared to the control group ($P<0.05$), but despite the difference between the case and control groups in the FEV1/FVC ratio, this difference was not statistically significant ($P=0.142$). Also in the study that D. Adekile et al., (15) aimed to investigate the association between PFT in children with SCD and increased fetal hemoglobin (HbF), it was shown that It was shown that FEV1 and FVC were lower in SCD patients than the control group, but there was no significant difference between FEV1/FVC ratio. In the present study, the results were similar to the findings of previous studies, so that in the control group,

FEV1, FVC and FEF25-75% were higher than patient group and this difference was significant ($P<0.001$), but FEV1/FVC ratio in the patient group was higher than the control group, but this difference was not significant ($P=0.187$). In the study, Achigbu et al., (14) in pulmonary function of children with sickle cell anemia compared to the control group showed that the mean of FVC, FEV1/FVC, PEFR and FEV1 was higher in the male control group compared to the male patients group, but this difference was not statistically significant and the only difference between FEV1 values was significant ($P=0.042$) However, in the female control group, the levels of FEV1, FVC and PEFR were significantly higher than those of HbSS women and this difference was significant ($P=0.006$, $P=0.01$ and $P=0.0035$, respectively), but the difference in FEV1/FVC ratio was not significant among the women in patients and control groups. In the present study, the results by gender were that in women the levels of FEV1, FEF25-75% and FVC were higher in the control group compared to the patients group and this difference was significant ($P<0.001$, $P<0.001$ and $P=0.004$, respectively). In the case of FEV1/FVC ratio, it should be said that this rate is almost equal among women in both case and control groups and there was no significant difference ($P=0.943$). Also, in men, FEV1, FEF25-75% and FVC values were higher in the control group compared to the patients group and this difference was significant ($P<0.001$). However, there was no significant difference in FEV1/FVC ratio between case and control groups ($P=0.137$). In our study, there was a difference in gender by interpreting the mean pulmonary function tests in the case group, but FEF25-75% and FEV1/FVC in the case group were more than men. However, there was no significant difference between men and women in FEV1, FEF25-75%, FVC and FEV1/FVC parameters. In our study, the results of comparing the mean pulmonary function tests of the case and control groups by age were obtained that in the age group less than or equal to 30 years, the values of FEV1, FEF25-75% and FVC in the control group were higher

than the case group and this difference was also significant ($P=0.002$, $P=0.001$ and $P=0.025$, respectively). There was no significant difference between the two groups in terms of FEV1/FVC ratio ($P=0.943$). Also, this comparison in the age group of people over 30 years of age showed that FEV1, FEF25-75% and FVC values were higher in the control group compared to the case group and this difference was more significant than the group under 30 years ($P=0.001$, $P=0.008$ and $P<0.001$, respectively). However, there was no significant difference between the two groups in terms of FEV1>/FVC ratio ($P=0.715$). In this study, comparing the mean pulmonary function tests in two age groups less than or equal to 30 years and over 30 years in the case group, the results also showed that the amounts of FEV1, FEF25-75% and FEV1/FVC in the age group less than 30 years are more than the age group more than 30 years, but the amount of FVC in the age group is more than 30 years, however, the amount of FVC in the age group is more than 30 years, however, the amount of FVC in the age group is more than 30 years. However, there is no significant difference between FEV1, FEF25-75%, FVC and FEV1/FVC parameters in these two age groups. In the study, Achigbu et al., (14) in pulmonary function of children with sickle cell anemia in 6-10 years old and 11-20 years old compared to the control group was shown to be FEV1, FVC and PEFR rates of all three increase with age and this increase is always higher in the control group than in the case group. The difference in FEV1 values was significant only in the age group of 6-10 years, the difference in FVC values was not significant in any age group and the difference in PEFR values increased with age and in the age group of 11-20 years was more significant than the age group of 6-10 years ($P=0.007$ and $P=0.024$). Now, according to our findings in the present study and comparing it with the findings of Achigbu et al., (14) study, it can be found that functional lung tests in the group with sickle cell anemia with age decrease, which made this difference more significant between age groups.

Conclusion

The results of this study showed that FEV1, FVC and FEF25-75% in the control group were higher than these values in the patient group and this difference was significant, although the FEV1/FVC ratio in the patient group was higher than the control group, but this difference was not significant.

Suggestions

- 1) Considering the low sample size compared to other studies, which were obtained during the desired period of time, it is suggested that this study be conducted in a longer period of time.
- 2) Since TLC and other pulmonary volumes are likely to be effective in finding the cause and pathogenesis of pulmonary disorders in SCDs (16), it is suggested that in subsequent studies these pulmonary volumes be measured and compared between case and control groups.
- 3) Since a large number of patients referred to centers except Shahid Mohammadi hospital in Bandar Abbas and therefore the number of patients studied decreased, it is suggested to use other centers such as private offices to participate in future studies.

Limitations

- 1) A large number of patients referred to centers except Shahid Mohammadi hospital clinic in Bandar Abbas, so a number of patients were not included in the study.
- 2) Some of the patients did not have proper cooperation to enter the study, so a number of patients were not included in the study.

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