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Soft-tissue profile characteristics in children with beta thalassaemia major

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Abstract

Objectives: To compare soft-tissue profile characteristics of patients with beta thalassaemia major (BTM) with a group of non-thalasseamic subjects with a similar skeletal pattern. ***Subjects and methods.*** The material for this cross-sectional retrospective study consisted of lateral cephalograms of 40 BTM patients (23 males, 17 females, aged 9.5 ± 0.97 years). These were compared with lateral cephalograms of a control group of 40 non-thalasseamic subjects (23 males, 17 females, aged 11.0 ± 0.87 years) who had similarities with the study group in the following cephalometric variables: SNA (°), SNB (°), ANB (°) and anterior face height (N-Me). Overall, 22 linear and angular soft-tissue cephalometric variables were measured. ***Results.*** Horizontal soft-tissue measurements, except for the thickness at B point (B-B'), were larger relative to non-thalasseamic subjects; particularly showing a statistically larger mean values for the following variables: soft-tissue thickness at Pronasale (ANS-Prn, $p < 0.01$), Subnasale (ANS-Sn, $p < 0.01$), point A (A-A′, $p < 0.01$) and at the Pogonion point (Pg-Pg′, $p < 0.05$). Compared to controls, BTM patients showed significantly larger ($p < 0.05$) mean values for the anterior nose length (Prn-Prn', $p < 0.01$) and lower nose height (Prn-Sn, $p < 0.05$). Variables that represented the lip profile, including the nasolabial angle, did not significantly differ from controls. The average values for the mid-face (N-ANS), posterior face height (S-Go) and the inclination of maxillary incisors to the SN plane were significantly larger ($p < 0.01$) in BTM patients. ***Conclusion:*** The soft-tissue profile differences in BTM patients may have implications for their future orthodontic or orthognathic management. Future studies can investigate the 3D soft-tissue changes and the possible contributing factors.

Key Words: *beta thalassaemia major, soft-tissue profile, cephalometry*

Introduction

Thalassaemia is a hereditary disease, leading to severe and chronic hemolytic anemia that results from mutations affecting the hemoglobin synthesis (α or β polypeptide chains of hemoglobin) [1–3]. The heterozygous form of the disease is usually asymptomatic and mild (minor), but the homozygous form, the beta thalassaemia (thalassaemia major), shows the most severe symptoms [1–3]. The beta-thalassaemia, also known as Cooley's anemia, causes severe anemia and if left un-treated can lead to serious consequences [4,5] and is characterized by severe anemia that begins months after birth [6].

These patients frequently suffer from growth abnormalities, bone deformities and hepatosplenomegaly [1]. Patients with beta thalassaemia major (BTM) show some altered craniofacial features [4,5] such as the vertical growth direction of mandible and short mandibular body and ramus length, leading to Class II malocclusions [3,7–11]. These changes can be because of ineffective erythropoiesis in patients with BTM, causing osteoporosis and extreme expansion of the marrow space in long bones, skull and facial bones [1]. This can lead to thinning of the cortical parts of the bones (osteoporosis) and pathologic fractures [12]. Among other features are prominent frontal and parietal bones, a depressed

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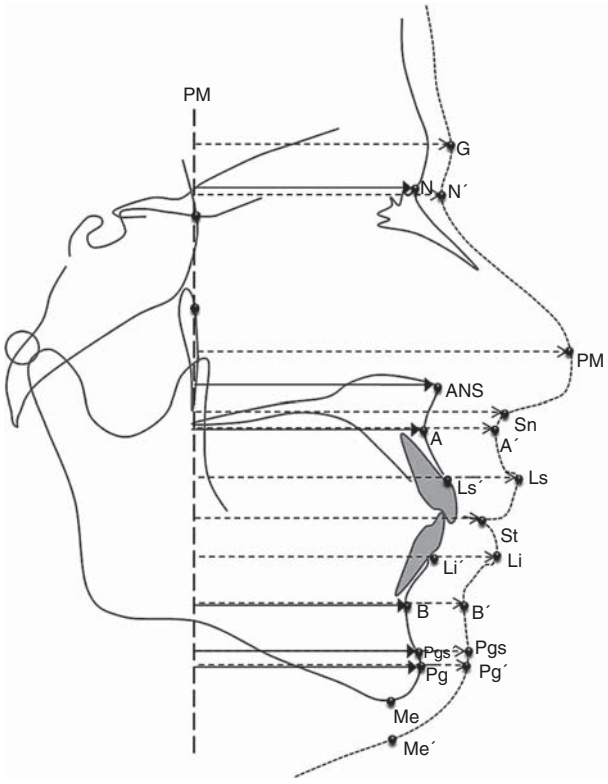

Figure 1. Landmarks and the reference planes used: S, Sella; N, Nasion; N′, soft-tissue Nasion; ANS, Anterior Nasal Spine; Prn, Pronasale; Sn, Subnasale; A, point A; A′, projected A point; Ls, Labrale superius; Li, Labrale inferius; St, Stomion; B, point B; B′, projected B point; Pg, Pogonion; Pgs, soft-tissue Pogonion; Pg′, projected Pogonion; Pgs′, projected soft-tissue Pogonion; Me, Menton; Me′, soft-tissue Menton; Ls′, projected Labrale superius; Li′, projected Labrale inferius; PM, Posterior Maxillary plane.

bridge of the nose and the characteristic mongoloid eye cant [13]. The prominent premaxilla and zygomas and cheekbones may also lead to the 'Rodent' facial characteristics in these patients [14,15]. Further, expanding facial bones in infancy and early childhood may inhibit pneumatization of the maxillary sinuses [2,13] and maxillary alterations can laterally displace the orbits, leading to hypertelorism, pseudo-overgrowth or a hypertrophied and procumbent maxilla [2,13].

Previous studies [3,7,9,16,17] emphasized mostly on the skeletal changes in patients with BTM and only a few studies [8,11] evaluated the soft-tissue structures of these patients. However, they used limited soft-tissue measurements and different methodologies and, therefore, applicability of their findings in other populations is questionable. The aim of the present study was to investigate the facial soft-tissue profile characteristics of patients with BTM major in an Iranian population and to test the null hypothesis that there is no difference between the soft-tissue profile of patients with BTM and the non-thalassaemic subjects with a similar skeletal pattern.

Subjects and methods

Study group

Ethical approval for the present cross-sectional retrospective study was obtained from the Islamic Azad Dental College Research Ethics Committee. The material for this study comprised of lateral cephalograms of 40 patients with BTM (23 males and 17 females, aged 9.5 ± 0.97 years) who were referred from the Ali Asghar Hospital for an assessment at the Department of Orthodontics, School of Dentistry, Islamic Azad Medical University. The Ali Asghar Hospital is a major treatment center for patients with thalassemia in Tehran, Iran.

The selection criteria for the present study were:

(1) Subjects between 8–14 years old diagnosed with BTM;
(2) Iranian nationals;
(3) No history of craniofacial surgical interventions or previous orthodontic treatment; and
(4) No additional associated medical syndromes or history of trauma to the head and neck region.

Subjects and their parents/guardian were given information regarding the objectives of the study and written consents were obtained from the parents or guardian of the patients. As an incentive, all patients were given a free orthodontic consultation (including the cost of radiological examination) by the attending orthodontist.

Control group

Forty non-thalasseamic subjects (23 males and 17 females, aged 11.0 ± 0.87 years) were selected from the archives of the Department of Orthodontics, School of Dentistry, Islamic Azad Medical University. The BTM patients tended to show Class II skeletal relationships (ANB > 5) [7]. Subjects for the control group were selected to have similarities with the study group for the following cephalometric variables: SNA (°), SNB (°), ANB (°) and anterior face height (N-Me).

Cephalometric measurements

All cephalograms were taken with the patient's lips in a relaxed position and their head oriented at the true horizontal line. The relaxed lip position was necessary to accurately assess the relationship of soft-tissues relative to hard tissues without muscular compensation for dentoskeletal disharmonies [18,19]. The magnification for cephalograms was 8.2%, but no correction was done as cephalograms for study and control groups were taken using the same cephalostat machine (Planmeca Proline EC). Cephalograms were hand traced using the orthodontic tracing paper on a conventional light box with a 0.3 mm lead pencil. Hard and soft-tissue cephalometric landmarks were

registered (Figure 1). The Posterior Maxillary (PM) plane was used as a reference line [20], which was perpendicular to the true horizontal line. The soft-tissue variables in the antero-posterior (horizontal) and vertical dimensions were measured and recorded (Figure 2). The nose and lips were also evaluated by measuring other linear and angular cephalometric variables (Figure 3). Additionally, the uvulo-glosso-pharyngeal dimensions in the present study sample were measured and reported using the same cephalometric films [21].

Statistical analysis

Fifteen randomly selected cephalograms were traced twice, 1 week apart, and measurements used to assess the reliability of the investigator (FA). Reliability of the method for first and second measurements was assessed using the Spearmen's correlation coefficients (rho), which ranged from 0.896–0.922 for different cephalometric measurements. Further, no significant differences ($p > 0.05$) were found between the first and second measurements of cephalometric variables (using the paired *t*-test). Statistical analyses were performed with SPSS (V. 17) and α was set to 0.05. The differences between patients with BTM and non-thalasseamic subjects were assessed using the independent *t*-test.

Results

Soft-tissue thickness

All horizontal soft-tissue variables in patients with BTM, except for thickness at the B point (B-B′), were on average larger relative to the non-thalasseamic subjects (Table I). The differences were only significant for the following measurements: ANS-

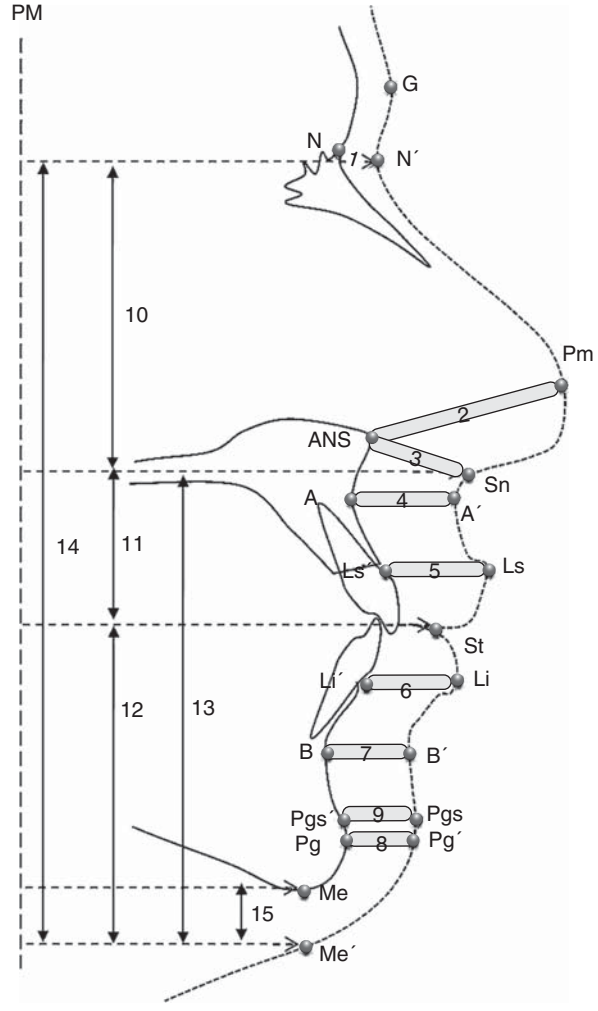

Figure 2. Linear variables for evaluation of the sagittal and vertical soft-tissue thicknesses: (1) Nasion (N-N′); (2) Pronasale (ANS-Prn); (3) Subnasale (ANS-Sn); (4) Point A (A-A′); (5) Labrale superius (Ls′-Ls); (6) Labrale inferius (Li-Li′); (7) Point B (B-B′); (8) Hard-tissue Pogonion (Pg-Pg′); (9) Soft tissue Pogonion (Pgs-Pgs′); (10) Mid-face height (N′-Sn); (11) Upper lip height (Sn-St); (12) Lower lip height (St-Me′); (13) Lower face height (Sn-Me′); (14) Total face height (N′-Me′); (15) Soft-tissue thickness in Menton (Me-Me′).

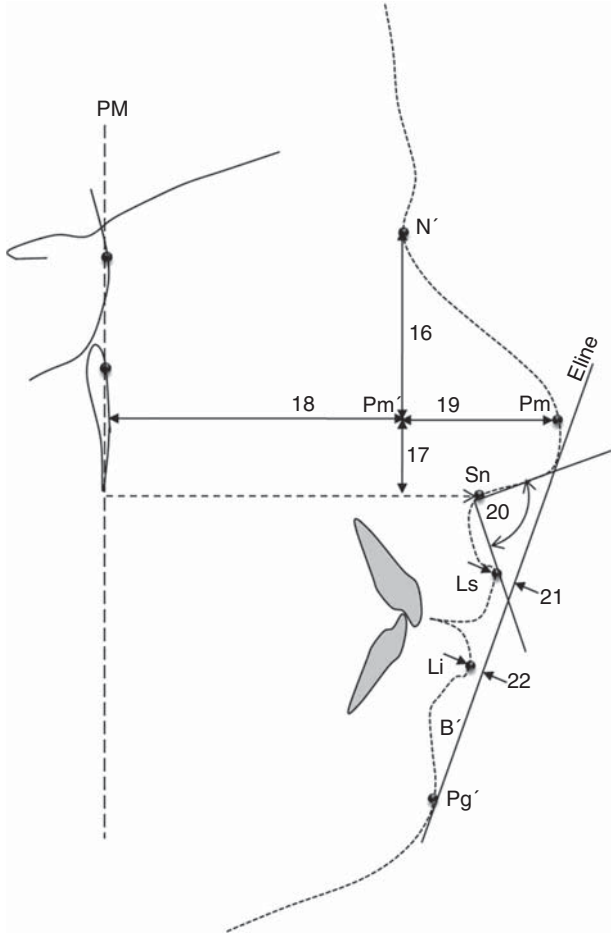

Figure 3. Linear and angular measurements of nose and lips. (16) Upper nose height (N′-Prn′); (17) Lower nose height (Prn′-Sn); (18) Posterior nose length (PM plane-prn′); (19) Anterior nose length (prn′-prn); (20) Nasolabial angle; (21) Ls-E line; 22. Li-E line.

Table I. Descriptive analysis [mean, Standard Deviation (SD) and 95% Confidence Interval (CI) of the mean] and the results of the independent *t*-test for soft-tissue cephalometric variables (horizontal and vertical variables) between thalasseamic patients and controls.

	Thalassaemics ($n = 40$)		Controls ($n = 40$)		
Soft-tissue variables (mm)	Mean (SD)	95% CI	Mean (SD)	95% CI	*p*-value
Horizontal variables					
Na-Na′	7.07 (2.02)	6.42–7.72	6.26 (2.48)	5.47–7.05	NS
ANS-Prn	26.36 (4.52)	24.91–27.81	20.10 (2.47)	19.31–20.89	**
ANS-Sn	14.89 (5.75)	13.05–16.73	9.26 (3.25)	8.22–10.30	**
A-A′	15.94 (3.84)	14.71–17.17	11.19 (2.43)	10.41–11.97	**
Ls-Ls′	13.57 (2.05)	12.91–14.23	12.47 (3.36)	11.40–13.54	NS
Li-Li′	16.57 (2.71)	15.70–17.44	15.05 (2.62)	14.21–15.89	NS
B-B′	12.84 (3.59)	11.69–13.99	13.05 (2.87)	12.13–13.97	NS
Pg-Pg′	11.39 (2.43)	10.61–12.17	9.73 (2.37)	8.97–10.49	*
Pgs-Pgs′	13.55 (3.21)	12.52–14.58	13.31 (3.91)	12.06–14.56	NS
Vertical variables					
N′-Sn	49.63 (10.64)	46.23–53.03	47.18 (5.65)	45.37–48.99	NS
Sn-St	23.84 (3.91)	22.59–25.09	23.73 (2.32)	22.99–24.47	NS
St-Me′	46.42 (5.20)	44.76–48.08	46.76 (4.82)	45.22–48.30	NS
Sn-Me′	70.13 (7.42)	67.76–72.50	70.60 (8.62)	67.84–73.36	NS
N′-Me′	120.91 (11.94)	117.09–124.73	118.05 (8.62)	115.29–120.81	NS
Me-Me′	7.92 (5.27)	6.23–9.61	6.73 (1.61)	6.22–7.24	NS

NS, Non-significant.
* $p < 0.05$; ** $p < 0.01$.

Prn ($p < 0.01$), ANS-Sn ($p < 0.01$), A-A′ ($p < 0.01$) and Pg-Pg′ ($p < 0.05$). Therefore, the null hypothesis for this study was partially rejected. Most vertical soft-tissue measurements showed no significant differences between the two groups (Tables I and II).

Linear and angular measurements of the nose and lips

Compared to the control group, patients with BTM showed significantly larger average values for the anterior nose length (Prn-Prn′) ($p < 0.01$) and the lower nose height (Prn-Sn) ($p < 0.05$). In general, the linear and angular variables that represent the lip profile, including the nasolabial angle, did not significantly differ between groups (Table II).

Dentoskeletal cephalometric variables

The mid-face (N-ANS) and the posterior face height (S-Go) were on average larger in patients with BTM ($p < 0.01$ for both). The angle between the maxillary centrals and the SN plane ($p < 0.01$) and the interincisal angle ($p < 0.05$) were on average larger and smaller in the thalasseamic group, respectively (Table II).

Discussion

Various forms of thalassemias have been found in most ethnic groups and geographic locations; most common in the Mediterranean basin and equatorial regions of Asia and Africa [13]. It comes with major, intermediate, and minor forms, with multiple complex genetic mutations (more than 100) responsible for these three categories [2]. The present study was designed to compare the soft-tissue profile of patients with BTM with a control group with similar skeletal patterns. The sample age range was selected as this was the common age for starting the orthodontic treatment (9.5 ± 0.97 years). To our knowledge, there were no previous reports on soft-tissue characteristics of Iranian children diagnosed with thalassaemia. Relying on the cephalometric dentoskeletal analysis for treatment planning can sometimes lead to esthetic problems, particularly when the orthodontist tries to predict soft-tissue outcome using only hard tissue normal values [22]. Many patients with severe form of thalassaemia ultimately need orthodontic and orthognathic correction and detailed information about the soft-tissue profile in these patients is valuable. Previous soft-tissue studies of thalassaemia patients used either angular or very limited measurements [8,11], providing incomplete information about soft-tissue changes in these patients. For instance, the recent study of Toman et al. [11] only used few measurements to investigate this topic. Considering that many of these patients eventually need orthodontic and orthognathic management, we felt that detailed description of the soft-tissue profile is needed. This study primarily assessed the soft-tissue thickness (excluding the Nasolabial

Table II. Comparison of soft-tissue measurements (mean, SD and 95% CI of the mean) of the nose and lips as well as dentoskeletal characteristics between thalasseamic patients and controls.

	Thalassaemics (n = 40)		Controls (n = 40)		
Variables	Mean (SD)	95% CI	Mean (SD)	95% CI	p-value
Nose					
N′-Prn′ (mm)	38.00 (4.51)	36.56–39.44	35.52 (5.02)	33.91–37.13	NS
Prn′-Sn (mm)	13.34 (2.12)	12.66–14.02	11.71 (1.57)	11.21–12.21	*
PM-Prn′ (mm)	49.78 (4.84)	48.23–51.33	48.63 (6.15)	46.66–50.60	NS
Prn′-Prn (mm)	29.57 (4.19)	28.23–30.91	23.44 (4.22)	22.09–24.79	**
Lips					
Nasolabial angle (°)	106.63 (11.28)	103.02–110.24	102.97 (16.29)	97.76–108.18	NS
Ls - E line (mm)	−1.84 (2.54)	−2.65– (–1.03)	−2.62 (3.12)	−3.62– (–1.62)	NS
Li - E line (mm)	1.36 (4.47)	−0.07–2.79	3.07 (3.12)	2.07–4.07	NS
Dentoskeletal					
MP (°)	37.83 (3.42)	36.74–38.92	40.10 (6.44)	38.04–42.16	NS
N-ANS (mm)	52.76 (4.18)	51.42–54.10	47.55 (4.43)	46.13–48.97	**
ANS-Me (mm)	67.55 (5.55)	65.78–69.32	67.89 (5.55)	66.12–69.66	NS
N-Me (mm)	120.55 (8.38)	117.87–123.23	116.68 (7.17)	114.39–118.97	NS
S-Go (mm)	76.77 (6.02)	74.84–78.70	68.68 (5.94)	66.78–70.58	**
ANB (°)	7.55 (1.75)	6.99–8.11	7.36 (2.09)	6.69–8.03	NS
SNA (°)	80.39 (4.81)	78.85–81.93	79.34 (3.31)	78.28–80.40	NS
SNB (°)	72.84 (4.45)	71.42–74.26	71.97 (3.73)	70.78–73.16	NS
Overjet (mm)	5.76 (2.10)	5.09–6.43	4.92 (1.61)	4.41–5.43	NS
Max Incisors-SN (°)	104.36 (6.64)	102.24–106.48	95.28 (8.83)	92.46–98.10	**
Man Incisors-MP (°)	101.13 (5.83)	99.27–102.99	99.89 (8.16)	97.28–102.50	NS
Inter-incisal (°)	115.13 (6.78)	112.96–117.30	121.75 (8.20)	119.13–124.37	*

NS, Non-significant.
* $p < 0.05$; ** $p < 0.01$.

angle and few other hard-tissue angular measurements) in the patients with BTM. In comparison with previous studies [8,11], we mainly used linear measurements to assess changes in soft-tissue covering the skeletal bases.

A comparison of our findings with the previous studies [8,11] is difficult due to different methodologies and samples used. Soft-tissue variables such as the thickness of upper and lower lips and the Nasolabial angle are important components of facial esthetics [22]. In the present study, the thickness of these landmarks was on average greater in the thalassaemia compared to controls; statistically significant changes were observed in the soft-tissue thickness of upper lip, nose and at the Pogonion point. Toman et al. [11] also observed protrusion of the upper and lower lips with a significantly acute Nasolabial angle in the thalasseamic patients. This is an important finding and can potentially affect the future orthodontic and orthognathic management of these patients. It is not clear if these changes are specific to the present Iranian patients with thalassaemia or occur widely in most thalassaemia patients. Currently, our understanding of these characteristics is limited and future multi-center studies of other populations can properly address this question. Interestingly, the mean value of the Nasolabial angle for our sample was not significantly different from patients with Class II skeletal pattern, but was greater (106°) than the reported figure of Toman et al. [11] (87.2°). This reveals distinct differences between the soft-tissue profile of our study group and the Malaysian study group [11].

One of the objectives of this study was to compare patients with BTM with patients of similar skeletal pattern. The recent study showed that, although these patients have a Class II skeletal pattern, but components of this Class II skeletal relationship were quite different from the control group that we used, as reflected by significant differences in the linear measurements of the mid-face (N-ANS) and the posterior face height (S-Go) in patients with BTM. Comparison with a group of Class I skeletal [11] or normal individuals probably would not have revealed these differences. The larger values of the anterior nose length (Prn'-Prn) and lower nose height (Prn'-Sn) probably indicate that nasal soft tissue (nose size) is

more prominent in patients with BTM, compared to non-thalassaemia patients with similar skeletal patterns. The present finding is that the thickness of the soft-tissue profile in patients with BTM has implications for orthognathic management of these patients. The severe form of BTM often requires orthognathic management to correct the skeletal discrepancy with procedures such as the Le Fort I maxillary osteotomy and recontouring of the lateral maxilla, for correction of maxillary excess and mandibular osteotomies, genioplasty and chin augmentations, to address the chin or mandibular deficiency [13,23,24]. These procedures affect the soft-tissue profile and detailed knowledge about the of soft-tissue characteristics is required for successful management. However, longitudinal studies or measurement comparison with a control group of an older age is needed to determine if present soft-tissue differences exist at the completion of skeletal growth, when orthognathic surgery is done. One of the limitations of the study was the use of a 2D representation of the 3D structure for assessing the soft-tissue. Considering the likely orthognathic need in patients with BTM, investigations using the less invasive radiography (Cone beam) or the 3D laser scanner can help evaluate the 3D soft-tissue changes more accurately.

Conclusion

Our findings suggest there are soft-tissue profile differences between the thalasseamic patients and controls with a similar skeletal pattern. The soft-tissue differences in patients with BTM may have implications for their future orthodontic or orthognathic management. Future studies can investigate the 3D soft-tissue changes and the possible contributing factors.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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