Reference Equations for Static Lung Volumes and TL_{CO} from a Population Sample in Northern Greece

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Key Words

Prediction equations · Pulmonary diffusing capacity · Pulmonary function testing · Residual volume · Total lung capacity · Transfer factor of the lung for CO

Abstract

Background: The most commonly used reference equations for the measurement of static lung volumes/capacities and transfer factor of the lung for CO (TL_{CO}) are based on studies around 30–40 years old with significant limitations. **Objectives:** Our aim was to (1) develop reference equations for static lung volumes and TL_{CO} using the current American Thoracic Society/European Respiratory Society guidelines, and (2) compare the equations derived with those most commonly used. **Methods:** Healthy Caucasian subjects (234 males and 233 females) aged 18–91 years were recruited. All of them were healthy never smokers with a normal chest X-ray. Static lung volumes and TL_{CO} were measured with a single-breath technique according to the latest guidelines. **Results:** Curvilinear regression prediction equations derived from the present study were compared with those that are most commonly used. Our reference equations in accordance with the latest studies show lower values for all static lung volume parameters and TL_{CO} as well as a different way of deviation of those parameters (i.e. declining with age total lung capacity, TL_{CO} age decline in both sex and functional

residual capacity age rise in males). **Conclusions:** We suggest that old reference values of static lung volumes and TL_{CO} should be updated, and our perception of deviation of some spirometric parameters should be revised. Our new reference curvilinear equations derived according to the latest guidelines could contribute to the updating by respiratory societies of old existing reference values and result in a better estimation of the lung function of contemporary populations with similar Caucasian characteristics.

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Introduction

Measurement of static lung volumes and lung diffusing capacity is frequently an integral part of the functional assessment of patients with lung, chest wall, and cardiac or respiratory muscle impairments. The determination of static lung volumes is essential for the diagnosis of restrictive, obstructive or mixed ventilatory defects [1]. In obstructive defects, it may also help to disclose underlying diseases (i.e. asthma air trapping vs. emphysema), to evaluate their functional consequences (i.e. the magnitude of capilloalveolar destruction in emphysema), and to assess their severity and disease progress [1–3].

It is well known that existing studies for both static lung volumes and diffusing capacity were performed at

least two or three decades ago showing remarkable discrepancies in predicted values among different authors [4, 5]. Such differences may be ascribed to the selection of subjects, methodological and technical differences in the assessment and variability due to the inclusion of different ethnic groups. Due to the fact that most of the studies were performed many years ago, they may not fit present-day anthropometric characteristics because of cohort effects.

Although new studies concerning dynamic lung volumes and flows abound, there is a considerable lack of newest data for static lung volumes and diffusion capacity. In practice, many USA and European laboratories use the reference equations for total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV) recommended by the 1995 American Thoracic Society (ATS)/European Respiratory Society (ERS) workshop [5] or by the European coal and steel community [6, 7]. Those reference values derive from a process of conjunction of different published reference equations and not from original data. To get a glimpse of these discrepancies, one can have a look at the diagrams of our figures. Different studies used various selection criteria, methodologies, statistical analyses, and some of them did not exclude smokers or ex-smokers as a rule. Most of these studies included a very small number of healthy subjects (around 250 at most for both sexes) [8–10], did not strictly comply with the existing recommendations for spirometry, were carried out over 30 years ago and incorporated all the inconsistencies that arise from the use of variously defined normal groups. Finally, the lung function decline with age seen in longitudinal studies differed significantly from that predicted from cross-sectional studies [11–13], suggesting that data from them reflect the population of that time and are valid only for a limited time period, before population changes render them obsolete. Changes in lung function in the last decades are obvious in new published data, mainly in the aged population.

We took the opportunity to provide a comprehensive set of lung function prediction equations for static lung volumes and TL_{CO} of both sexes based on contemporary technical and statistical methods with rigorous selection criteria for normal subjects.

Materials and Methods

Study Population

Subjects were recruited from an area of Northern Greece over 4 years from September 2009 to September 2013. Participants were volunteers of Caucasian origin aged 18–91 years, and were recruit-

Table 1. Exclusion criteria

History of smoking >1 pack-year
Acute respiratory disease
Upper and/or lower respiratory tract infection
Common cold
Respiratory symptoms during the last 6 months
Wheeze
Cough
Phlegm
Dyspnea at rest or during minimal exercise
History of respiratory disorders
Chronic obstructive pulmonary disease
Asthma
Pulmonary embolism
Pulmonary fibrosis
Sarcoidosis
Current use of bronchodilators
Patients with abnormal spirometry
Heart failure and/or coronary heart disease
Use of other drugs (diuretics, inotropic)
Anemia, erythrocytosis, hematological diseases
Morbid obesity (BMI >35)
Abnormal chest radiographs
Major ECG abnormalities
Institutionalized; terminal illness
Inability to walk, communicate, or give informed consent
History of chest injuries
Exposure to substances known to cause lung injury
History of other chest diseases
Lung cancer
Lung surgery
Kyphoscoliosis
Neuromuscular disorders

ed as part of another larger epidemiological study. The selection was compatible with recently issued ATS/ERS recommendations [1] which consider valid and acceptable reference values derived from large groups of volunteers, provided of course that the criteria for proper selection and distribution of anthropometric characteristics are met. The study has been approved by the ethical committee of the Medical Department of Aristotle University of Thessaloniki (No. 2-27/3/2013) and an informed consent form was signed by all the examined subjects.

For screening, strict selection criteria were applied including completion of a validated for the Greek population questionnaire [14, 15], a chest X-ray and an electrocardiography. Detailed exclusion criteria are described in table 1.

Methods

Lung function testing was performed in the Lung Function Laboratory of the Pulmonary Department of Aristotle University (Papanicolaou General Hospital, Thessaloniki, Greece) between

9 a.m. and 2 p.m. All tests were performed by a single technician (N. Tsekouriadis) with 30 years' experience in lung function testing. The spirometer used is Masterscreen PFT (version 4.3 of Jaeger GmbH), with a pneumotachograph which satisfies ATS/ERS requirements and is at least once daily calibrated in accordance with the manufacturer's instructions. Standing height was measured without shoes, with the subjects' back to a vertical backboard. Subjects were weighed whilst wearing indoor clothing without shoes, and body mass index ($BMI = \text{weight}/\text{height}^2$; expressed in $\text{kg} \cdot \text{m}^{-2}$) and body surface area ($BSA = 0.20247 \times \text{height}^{0.725} \times \text{weight}^{0.425}$; expressed in m^2) were calculated. Age was recorded to the nearest birthday.

All spirometric measurements were performed in a sitting position. The technician first demonstrated the test procedure to the individual tested. Lung volumes were measured using the single-breath technique properly modified for the simultaneous measurement of TL_{CO} and all the subdivisions of TLC [16], according to manufacturer's instructions (http://www.carefusion.de/pdf/Respiratory/Pulmonary_Function_Testing/CO_Diffusion_Single_Breath.pdf). Fixed dead space between the patient and the unit sampling was 50 ml. A standard anatomic dead space of 150 ml was used in the evaluated data. Prior to this, each subject had a vital capacity (VC) measurement.

The TL_{CO} single breath maneuver is the most commonly used method for the measurement of TL_{CO} and begins with unforced exhalation to RV. Then, subjects are vigorously coached to inhale a maximum VC of the test gas. This inhalation time should not exceed 4 s. Longer inhalation times should be noted. Test gas contained 9.2% He, 20.8% O_2 , 0.26% CO, and the rest was N_2 . The inspiratory VC should have been more than 90% of the subject's maximum VC. Then, subjects were instructed to keep their breath. The breath hold time should be 10 ± 2 s, a target easily achieved in the vast majority of subjects. The subject did not come off the mouth piece between the lung volume measurements and TL_{CO} , and the ATS/ERS standards for static lung volumes were followed.

TL_{CO} calculation assumes instantaneous lung emptying as it happens with the inspiration maneuver. Although various sample timing techniques address the fact that emptying is not instantaneous, it is still reasonable to expect that the expiratory maneuver should be smooth, unforced, without hesitation or interruption, and total exhalation time should not exceed 4 s (with sample collection time <3 s). The first 750 ml was wasted to wash out for the dead space. The next 750 ml of the expired air was collected for gas concentration analysis. All the units are physically collecting the sample.

The process was repeated once more with an interval of 5 min between the two measurements. TLC, FRC and RV were measured, and the average values were used for analysis. At least two measurements were performed, which had to agree to within 1 (mmol/min)/kPa or 10% in terms of TL_{CO} values, whichever was greater; otherwise, further measurements were made until repeatable results were obtained. All the results were corrected to body temperature and pressure-saturated units. We assume a mean standard hemoglobin concentration of 13.4 g/dl for women and 14.6 g/dl for men.

Statistical Analysis

In order to develop prediction equations, multiple linear and curvilinear regressions of each parameter of lung function were generated against combinations of the independent variables

height, age, weight, BMI and BSA. Regression equations were also calculated using transformations (χ^2 , $\sqrt{x}$, $\ln x$) of both the independent and dependent variables. We estimated prediction equations for the mean for each parameter examined. Prediction equations that have been proposed in the literature before were compared to ours graphically. Data analyses were performed using R 2.14.0 (2011-10-31).

In developing the regression model, age was found to be a necessary independent variable for all pulmonary function parameters. Height and weight were similar in terms of increasing R^2 , with little improvement when both are used in the model, height being chosen as the preferred measure. BMI and BSA offered improvements similar to weight. Therefore, only age and height were used in the reference equations.

Results

After selection of healthy nonsmoking subjects, a total of 234 males and 233 females were included in the study. All subjects completed successfully a VC and a TL_{CO} single breath maneuver with simultaneous TLC subdivision measurement. Four age groups were created: (a) 18–24 (young people); (b) 25–44 (young adults); (c) 45–64 (middle-aged adults); (d) 65+ (elderly). Demographic data of the 467 subjects as a whole and by age group are shown in tables 2 and 3 for men and women separately. On the basis of an equal representation, we had a minimum number of around 50 subjects for each age group.

The reference equations for static lung volumes, TL_{CO} and TL_{CO} /alveolar volume (V_A) = CO uptake from the lung (K_{CO}) of men and women separately are shown in table 4.

We use the formula below for every curvilinear equation of the predicted values like TLC, FRC, etc., for LNN (lower limit of normal) estimation

$$LLN = \text{predicted value} \cdot (1 - 1.654 \cdot rRMSE),$$

where rRMSE means relative root mean square error.

Comparisons with the reference equations for TLC, RV and FRC provided by ERS [6], Crapo et al. [9], Cordero et al. [17] and Garcia-Rio et al. [18] are shown in figures 1 and 2 for males and females, respectively. Comparison with the reference equations for TL_{CO} provided by Crapo et al. [19], Knudson et al. [20], Thompson et al. [21] and Aguilaniu et al. [22] is shown in figure 3 for males and females separately.

For RV, all studies provide similar equations both in terms of values and upward tendency when related to the age of the individuals (fig. 1b, 2b). The difference is that newest equations (ours and that of Garcia-Rio et al. [18]) give slightly lower values for both males and females. On

Table 2. Mean and standard deviation (SD) for age, height, weight, BMI and BSA for each age group and for the total number (men)

Age category		Age	Height, cm	Weight, kg	BMI, kg/m ²	BSA
18–24 years	Mean	19.5484	177.8871	80.9032	25.5434	1.9942
	SD	2.59051	6.24396	12.73012	3.66298	0.17396
	n	62	62	62	62	62
25–44 years	Mean	33.8026	179.8026	88.1316	27.2807	2.0947
	SD	5.50641	6.19897	10.79054	3.26231	0.14301
	n	76	76	76	76	76
45–64 years	Mean	53.3208	172.9245	90.3208	30.1338	2.0779
	SD	5.62198	7.02701	14.59686	3.95973	0.19220
	n	53	53	53	53	53
65+ years	Mean	73.9302	166.0233	79.6279	28.8651	1.9131
	SD	6.07256	5.54414	10.36483	3.33654	0.14237
	n	43	43	43	43	43
Total	Mean	41.8205	175.2051	85.1496	27.7578	2.0309
	SD	19.9635	8.04284	12.89305	3.91585	0.17650
	n	234	234	234	234	234

Table 3. Mean and SD for age, height, weight, BMI and BSA for each age group and for the total number (women)

Age category		Age	Height, cm	Weight, kg	BMI, kg/m ²	BSA
18–24 years	Mean	22.0816	165.7551	63.0408	22.9426	1.6999
	SD	0.83757	5.53598	9.38518	3.23950	0.13485
	n	49	49	49	49	49
25–44 years	Mean	34.6604	164.0189	68.5849	25.5468	1.7613
	SD	5.14387	6.50293	12.30140	4.73567	0.16486
	n	53	53	53	53	53
45–64 years	Mean	55.6667	156.4493	73.2899	29.9122	1.7800
	SD	5.56424	5.69710	11.58612	4.32918	0.15832
	n	69	69	69	69	69
65+ years	Mean	70.6129	153.3548	69.5484	29.5559	1.7174
	SD	4.89012	4.88254	10.11034	3.95620	0.13788
	n	62	62	62	62	62
Total	Mean	47.8026	159.3047	69.0687	27.3587	1.7422
	SD	18.9225	7.57303	11.46526	4.99048	0.15248
	n	233	233	233	233	233

the other hand, males demonstrate an accelerated upward tendency of RV after the age of 65 years (fig. 1b), whereas females show a plateau after that age (fig. 2b).

FRC measurements in females are similar for nearly all compared reference equations (fig. 2c); either stable or with a very slight upward tendency related to age. Regarding

ing males, a more pronounced upward tendency of FRC is observed especially after the age of 50 (fig. 1c).

TLC values in our study are clearly lower than in all other studies, except from the latest study by Garcia-Rio et al. [18], but there is also another major difference observed. Previous studies assume that TLC remains stable

Table 4. Predicted equations for static lung volumes and lung diffusing capacity for CO of men and women with R^2 and relative root mean square error (rRMSE)

Parameter	Equation	R^2	rRMSE
Men			
TLC, l	Exp [2.2633 ln (H) + 0.00585 · A – 7.228 · 10 ⁻⁵ · A ² – 9.9529]	0.583	0.104
FRC, l	Exp [2.34 ln (H) – 0.0049 · A – 7.4743 · 10 ⁻⁵ · A ² – 10.89]	0.135	0.226
RV, l	Exp [2.257 ln (H) + 0.01194 · A – 1.125 · 10 ⁻⁵ · A ² – 11.6819]	0.388	0.225
RV/TLC, %	Exp [0.026 ln (H) + 0.00464 · A – 7.44 · 10 ⁻⁵ · A ² + 2.7435]	0.61	0.187
FRC/TLC, %	Exp [0.07 ln (H) – 0.011 · A + 0.00015 · A ² + 3.71]	0.14	0.193
TL _{CO} , (mmol/min)/kPa	Exp [2.027 ln (H) + 1.44 · 10 ⁻⁶ · A – 6.266 · 10 ⁻⁵ · A ² – 7.96]	0.68	0.131
KCO, [(mmol/min)/kPa]/l	Exp [–0.258 ln (H) – 0.00517 · A + 4.01 · 10 ⁻⁶ · A ² + 2.1196]	0.351	0.122
Women			
TLC, l	Exp [2.246 ln (H) + 0.0064 · A – 9.386 · 10 ⁻⁵ · A ² – 9.99]	0.64	0.109
FRC, l	Exp [2.744 ln (H) + 0.0018 · A – 1.79 · 10 ⁻⁶ · A ² – 13.13]	0.188	0.23
RV, l	Exp [2.297 ln (H) + 0.02426 · A – 0.00015 · A ² – 12.131]	0.302	0.22
RV/TLC, %	Exp [0.0534 ln (H) + 0.018 · A – 5.69 · 10 ⁻⁵ · A ² + 2.4476]	0.61	0.189
FRC/TLC, %	Exp [0.4358 ln (H) – 0.0052 · A + 9.66 · 10 ⁻⁵ · A ² + 1.789]	0.1	0.204
TL _{CO} , (mmol/min)/kPa	Exp [1.887 ln (H) + 0.0075 · A – 0.00013 · A ² – 7.6155]	0.59	0.124
KCO, [(mmol/min)/kPa]/l	Exp [–0.324 ln (H) + 0.00218 · A – 5.325 · 10 ⁻⁵ · A ² + 2.207]	0.111	0.132

A = Age in years; H = height in cm.

across all ages, whereas ours and the latest studies reveal an accelerated decline of TLC with age, for both men and women.

Finally, TL_{CO} reference values in our study are similar to those of the recent study by Thompson et al. [21] and clearly lower compared to those that are most commonly used, for both sexes.

Discussion

We developed a new set of prediction equations for the measurement of static lung volumes and TL_{CO} for a wide age range of patients from a sample of asymptomatic Caucasians. To the best of our knowledge, our study is the largest all-age reference equation-deriving study for TL_{CO} and one of the largest for static lung volumes [17, 18]. The following basic criteria, required to obtain the reference values of static lung volumes and diffusion capacity, were fulfilled in our study: (1) a sufficient number of subjects for each sex with an equal representation of each age group; (2) strict inclusion criteria: healthy nonsmoking individuals from the mixed urban and rural populations; (3) standardization of measurements and quality control procedures according to the latest ATS/ERS recommendations, and (4) accurate statistical analysis.

Reference equations used today differ slightly from those used 20 years ago since there are no new studies

recommended by respiratory societies. Manufacturers had no new official data to incorporate into default equations and, as a result, most frequently used reference equations for static lung volumes, according to a survey in America [23], are those of Goldman and Becklake [8] from 1959. All those equations used as reference values are based on data from studies carried out over 30 years ago, and thus incorporate all the inconsistencies that arise from (1) variously defined normal groups (some include smokers), (2) morphological or technical differences, (3) different measurement procedures, (4) different instrumentation, (5) ethnic variations and (6) cohort effects.

We observed that there are major differences especially with the oldest studies which are more commonly used in both Europe and America. Some of the advantages of this study are: (1) it includes a sufficient number of subjects over 65 years old; thus, there is no need to extrapolate our results to older subjects, and (2) because of the curvilinear form of our prediction equations, we can point out special characteristics of lung function for different age groups.

The present study's equations differ from those derived from the ERS with regard to their mathematical form and to the nature of the underlying data. The ERS reference equations are linear and were obtained by summarizing published regression equations from older surveys published between the 1950s and 1980s that employed different instruments [6]. Our study is a prospec-

Fig. 1. Age dependency of mean values of TLC (a), RV (b) and FRC (c) in males (height 175 cm) in comparison with published reference values. Age range and subjects included in different studies. Present study: 18–91 years ($n = 234$); Cordero's group: 18–88 years ($n = 305$); Crapo's group: 15–91 years ($n = 123$); ERS: 18–70 years; Garcia-Rio's group: 65–85 years ($n = 132$).

tive one with curvilinear equations using a stable spirometer fulfilling ATS/ERS performance criteria, and all tests were carried out by a technician with 30 years of experience. The emphasis on quality control in our study may partly explain the different values observed when compared with other studies.

With regard to differences due to the technique used to determine lung volumes, it has been proposed to use the same reference values for plethysmographic and dilutional methods [5, 6]. The reference equations compared in our study were obtained from measurements, some with the single-breath helium dilution [9] method and

others with the multiple breath helium dilution [6] method. As stated by ERS, there are no differences between the two techniques when we refer to healthy nonsmokers. As far as plethysmography is concerned, it is well known that it overestimates lung volumes, especially in subjects with chronic obstructive pulmonary disease. Concerning healthy nonsmokers, dilution methods may slightly underestimate lung volumes in comparison to plethysmography.

There are some other differences in methodology between the studies compared: (1) the FiO_2 of the inspired mixture used (20.8% in the present study and 18–25% in

Fig. 2. Age dependency of mean values of TLC (a), RV (b) and FRC (c) in females (height 160 cm) in comparison with published reference values. Age range and subjects included in different studies. Present study: 18–85 years ($n = 233$); Cordero's group: 18–88 years ($n = 286$); Crapo's group: 17–84 years ($n = 122$); ERS: 18–70 years; Garcia-Rio's group: 65–85 years ($n = 189$).

other studies); (2) the compliance with the latest ATS/ERS recommendations for the determination of TL_{CO} (to the best of our knowledge only the studies of Thompson et al. [21], Aguilaniu et al. [22], Garcia-Rio et al. [24] and the present one comply with the latest recommendations), and (3) the different altitudes at which different studies have been conducted (ours at 670 m). All these issues hamper the objectivity of the between-study comparison.

Apart from the differences in predicted values of static lung volumes and TL_{CO} between the studies compared, which could be explained by the factors mentioned above,

there are some issues of high interest concerning our perception of deviation of different spirometric parameters.

For TLC of both sexes for example, in addition to height dependency, our reference equations confirm the importance of incorporating age in prediction equations as an independent variable. The reduction of maximal respiratory pressures in healthy elderly subjects [25] due to the age-related decrease in diaphragmatic strength [26] can consequently reduce inspiratory capacity. A reduction in diaphragmatic strength in healthy elderly subjects compared with young adults must have an effect on TLC [25].

Fig. 3. Age dependency of mean values of TL_{CO} in males (**a**) and females (**b**). In North America, the unit for DLCO is mLCO/min/mm Hg. In Europe, the SI unit is used (mmol/min/kPa) and the test is called TL_{CO} . The following equation converts between the 2 units. $DLCO = 2.986 \times TL_{CO}$. **a** Age range and subjects included in different studies. Present study: 18–91 years ($n = 234$); Aguilaniu's group: 18–94 years ($n = 161$); Crapo's group: 15–91 years ($n =$

123); Knudson's group: 25–84 years ($n = 71$); Thompson's group: 45–71 years ($n = 498$). **b** Age range and subjects included in different studies. Present study: 18–85 years ($n = 233$); Aguilaniu's group: 18–94 years ($n = 161$); Crapo's group: 17–84 years ($n = 122$); Knudson's group: 20–86 years ($n = 99$); Thompson's group: 45–71 years ($n = 474$).

On the other hand, an increase in RV is recognized as a result of (a) the increased closing volume in elderly [27], (b) age-related weakness of the expiratory muscles [28], (c) age-related diminished lung elastic recoil [29], and as an early feature of smoking-related lung disease [30], where the latter may have influenced the results of oldest studies [31, 32] which included ex-smokers. Our lower RV values may be attributed to the strict exclusion of ever-smokers, yet the accelerated increase rate in older males could be an effect of passive exposure to smoke or other occupational pollutants compared to older females, who stay mostly at home, not experiencing such predisposing exposure.

On the other hand, as TL_{CO} is concerned, our results are in close agreement with the latest study by Thompson et al. [21] (middle-aged adults) and with the latest data of Aguilaniu et al. [22] for over 60-year-old subjects. These differences (lower values in both males and females) with the oldest reference equations could possibly be attributed to the compliance with the latest ATS/ERS recommendations [33] and the use of modern equipment in the latest studies. The generally accepted theory that the decline in TL_{CO} follows a biphasic model 'relatively slow in young adults and faster in middle-aged adults', suggesting a reduction in the surface of the lung available for gas

exchange [34], seems to be confirmed in the present study. This phenomenon is better expressed by a curvilinear equation and illustrated in figure 3.

There are some limitations to our study. The wide age range of the examined subjects may result in some errors at the age extremes, especially at the oldest group which included fewer subjects compared to the other age groups. The use of healthy volunteers instead of a randomized sample could be a possible limitation. Another limitation is that not all measurements are calculated at sea level. To the best of our knowledge there is not a co-factor that is appropriate for predicted values at different altitudes. Only for TL_{CO} does each laboratory have to adjust measurements to its altitude according to MacIntyre et al. [33, equation 16]. Finally, the use of the single-breath technique (the most frequently used method for TL_{CO} measurements) could possibly impact the comparison between dilutional and plethysmographic methods, but this is inevitable when one method is chosen.

In conclusion, our set of prediction equations derived for a wide age range that is in accordance with the latest studies indicates the need for an update of reference equations for static lung volumes and lung diffusing capacity. Curvilinear correlations of all examined spirometric pa-

rameters are more suitable and correct in statistical terms. According to our findings, which are confirmed in the latest studies, there should be a decrease in absolute values for reference values of nearly all spirometric parameters (TLC, FRC, RV and TL_{CO}) and a change in our perception of deviation with age of some of those parameters, i.e. TLC and RV. Finally, this study fulfills the implementation of one source deriving reference equations for all spirometric parameters (dynamic and static lung volumes, lung diffusion capacity) suitable for a population of Greek descent and for populations of similar Caucasian characteristics.

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None declared by any of the authors.

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