Reference interval and upper decision limit for serum uric acid – an evidence-based approach on Romanian population using an a posteriori method

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Abstract

Introduction. There is accumulating evidence that high normal serum uric acid (SUA) levels of 6-7 mg/dL are associated with cardiovascular morbidity and metabolic syndrome (MetS), hence the need to redefine its upper limit of normal (ULN). We aimed to derive ULN based on statistics and evidence in a representative sample of the population and to observe its relation to MetS components. Methods. All SUA measurements form a university rheumatology hospital were extracted between January 5th 2010 and March 21st 2018. SUA levels were measured by a single biochemist a unique type of commercially available kit. Follow-up measurements, patients with diagnoses influencing SUA levels and outlying measurements were excluded. ULNs were studied using least square analysis. Results. Of the 22503 SUA measurements in the database, only 3318 came from normal individuals: 33.3% men (n=1105), 66.7% women (n = 2213). Least square analysis revealed the following SUA reference intervals (RI): 3.43-6.19 mg/dL for the combined sample; 4.44-7.01 mg/dL for men, 3.28-5.56 mg/dL for women. The values corresponding to the 66th percentile of each group presented lower ULNs: 5.36 mg/dL for all, 6.10 mg/dL for men, 4.90 mg/dL for women. The prevalence of hyperuricemia increased from 13.8% (manufacturer’s gender-specific ULN) to 19.9% (derived ULN). Mean SUA levels significantly increased with the number of MetS components. Conclusion. We recommend that hyperuricemia should be defined using a statistical approach of ULN selection corresponding to the gender- and population-specific 66th percentile of data range.

Keywords: hyperuricemia, serum uric acid, upper limit of normal, reference intervals

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Introduction

Humans possess a mutated, non-functional uricase [1], the enzyme which oxidizes uric acid to allantoin during purine catabolism. Serum uric acid (SUA) levels increase proportionally with taxonomical ranks [2]: monkeys and mammals have mean SUA levels below 3 mg/dL, while mean SUA levels in most human populations revolve around 6 mg/dL [3]. The most popular evolutionary hypothesis for this apparent gradual loss of uricase activity is that cumulative silencing mutations selected the beneficial antioxidant effect of uric acid [4], which, in turn, increased lifespan and protected the brain. However, Hershfield et al. [5] showed that treatment with pegloticase (a recombinant uricase produced by genetically engineered strains of Escherichia coli), in spite of dramatically lowering SUA levels (bellow 1 mg/dL), did not result in an increase of oxidative stress in gout patients, as expected in the absence of SUA. Rather, the antioxidant effect of uric acid seems to be a part of a more complex in vivo antioxidant strategy, which involves other endogenous antioxidants [6, 7]. The lack of human uricase activity does not seem to be a beneficial evolutionary loss, but rather a prerequisite design phenotype: the lowest means of SUA in humans are still twice as high as the highest means of SUA in uricase-lacking apes. Human biology seems to require a priori this additional amount of SUA since it uses a complicated, energy wasting, and apparently redundant mechanism of homeostasis [8]. Silencing mutations of uricase locus should have been concomitantly paralleled by enhancing mutations of renal and intestinal uric acid transporters in order for a person to remain normouricemic to a superior degree (multiple coherent antagonist mutations seem too convenient and statistically farfetched for any process of random speciation irrespective of time).

Since the rate of endogenous purine catabolism is generally constant (approximately 300-400 mg/day [9]), and since it explains most of SUA levels in the absence of uricase, any excess uric acid production in healthy subjects can originate either from high purine dietary intake, which is now a generalized characteristic of Western diets [2], or from unrecognized/subclinical metabolic disease processes. Since contemporary diets [10] have spread to most conservative societies, it is possible that laboratory SUA tests actually measure the expression of this culinary shift, rather than baseline physiological turn-over of purines. All SUA test manufacturers report an upper limit of normal (ULN) of around 7 mg/dL in men, which is above the solubility limit of monosodium urate (MSU) in body fluids in physiological conditions [9]. This reported ULN is correct, but most likely it does not estimate SUA normality, rather reflecting lifestyle/eating behaviour or confounding metabolic disease. The difference between a hypothetical mean normal level of SUA in a specific population and the current mean intake-biased higher levels of SUA probably is the determining factor for numerous epidemiological associations of SUA with disease other than gout. There is accumulating evidence that high normal SUA levels (6-7 mg/dL) are associated with incident metabolic syndrome (MetS) [11], cardiovascular risk [12], heart failure [13], cerebral ischemic pathology [14], new-onset hypertension among healthy adults [15], new-onset diabetes [16] and chronic kidney disease [17]. These observations led researchers [18, 19] to propose the revision of uric acid ULN to a value of 6 mg/dL, which theoretically better defines normouricemia.

In this context, we aim to observe if this newly proposed ULN is reflected in a large random population sample. Since SUA levels vary by race and ethnicity and since no previous data reported normal SUA levels from healthy Romanian subjects, the study also aims to estimate...
gender-specific reference intervals (RI) in a representative sample of Romanians, in order to define hyperuricemia, and to observe its relation to MetS components.

Methods

Database
The “Ion Stoia” Clinical Centre for Rheumatic Diseases (CCRD) is a rheumatology tertiary referral hospital in Bucharest, the capital of Romania. Patients from the entire country can be referred to CCRD by their general practitioners (for example, in 2013, only 25.6% of patients resided in Bucharest, while the rest came from all the other administrative regions of Romania). Since 2010, CCRD has been using an electronic database in which results of laboratory measurements are imputed automatically by analytical machine software, and are stored on the local server drive. Blood samples are obtained by standard peripheral venepuncture and are sent immediately to the laboratory for analysis. Before admission in the day-care or the in-patient department, each patient gives written informed consent regarding blood sampling and research use of medical data. With the approval of the local ethics committee, the laboratory database was searched for any data collected between January 5th 2010 (when CCRD started storing electronic records of laboratory results) and March 21st 2018.

Serum uric acid measurements
SUA levels were measured by a single biochemist with an Architect Plus C4000 machine (by Abbott®), using the manufacturer’s kits. The method of determination uses uricase and peroxidase in a two-part reaction to derive a quinoneimine dye from uric acid and then measure its absorbance at 604 nm. The machine was periodically calibrated and checked for quality using the manufacturer’s instructions. The manufacturer reports specific expected reference ranges in adults (3.5-7.2 mg/dL for men and 2.6-6.0 mg/dL for women) and performance characteristics for serum samples (limit of blank 1 mg/dL, limit of detection 0.06 mg/dL and limit of quantitation 0.22 mg/dL), with an imprecision level of ≤ 3.6% total coefficient of variation.

Data processing and statistics
The first step in data processing was to eliminate discharge diagnoses which were either known to influence SUA levels, or to be associated with high levels of SUA. These diagnoses were confirmed by the patient’s attending physician and recorded in the electronic database using disease codes based on the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Patients with the following categories of diagnoses were excluded (Figure 1): musculoskeletal diagnoses - infectious and reactive arthritis (M00-M03), rheumatoid arthritis (M05-M06), psoriasis (L40) and psoriatic arthritis (M07), gout and other crystal arthropathies (M10, M11), other forms of arthritis and arthropathies (M13-M14), systemic lupus erythematosus (M32), dermatopolymyositis (M33), systemic sclerosis (M34), other chronic systemic involvement of connective tissue (M35-M36), ankylosing spondylitis (M45-M46); cardiovascular diagnoses - obesity (E66), type 2 diabetes mellitus (T2DM; E10-E14), dyslipidaemia (E78), arterial hypertension (AHT; I10, I15), chronic heart failure (I11, I50), ischemic heart disease (I20-I25); chronic kidney disease (I12-I13, N18-N19) and cancer (C00-C97). Obesity, AHT, dyslipidaemia and T2DM were considered proximal components of MetS as defined by the International Diabetes Federation [20]. Using these diagnoses, 4 subgroups were formed: subjects with none of the 4 MetS components, patients with any one MetS component without all the others, patients with any two MetS components without all the oth-
ers, and patients considered to have the MetS (at least any three MetS components).
Within the database search timeframe, some patients had multiple SUA measurements, months and years apart. Therefore, the second step was to eliminate follow-up measurements, retaining only the first measurement for each person, prior to any therapeutic advice or intervention.
The third step was to eliminate outliers using the Hoffman method [21]. Values of SUA which fulfilled the following condition were labelled as outliers: $|\delta| > (\tau \cdot SD)$, where: $\delta = xi - m$;
$$\tau = \frac{t \cdot (n - 1)}{\sqrt{n \cdot (n - 2 + \tau^2)}}$$
(modified Thomson $\tau$), “SD” is the standard deviation of SUA measurements; “$xi$” represents each value of measured SUA; “$m$” is the mean of SUA measurements; “$n$” is the number of SUA measurements; “$t$” is the inverse of the two-tailed Student $t$ distribution calculated for a 0.05 probability and $n - 2$ degrees of freedom using TINV Excel function. The frequency of each SUA measurement ($xi$) was then determined by dividing the number of times that measurement appeared in the whole sample (count) with the sample number ($n$):
$$F_{Xi} = \frac{100 \cdot \text{count}_{Xi}}{n}$$
Subsequently, these values were summed in order to calculate cumulative frequencies of each SUA measurement
$$CF_{Xi} = \sum_{k=2}^{i} F_{Xi}$$
SUA measurements and their cumulative frequencies were then graphed in a line chart and the best-fitting linear regression was determined using least-squares analysis ($yi = \alpha \cdot xi + \beta + \epsilon i$; where “$\alpha$” is the slope of the regression line; “$\beta$” is the intercept of the regression line and “$\epsilon$” is the associated error) [22]. Considering that RI comprises values between 2.5% and 97.5% percentiles, the lower end of the RI was calculated as “$\alpha \cdot 2.5 + \beta$”, while the upper end of the RI was calculated as “$\alpha \cdot 97.5 + \beta$”.
Data distribution normality was assessed using descriptive statistics, normality and stem-and-leaf plots and the Lillefors-corrected Kolmogorov-Smirnov tests, which showed a normal distribution of age and SUA levels. The comparison of mean age and SUA levels, reported as “mean (standard deviation)”, were done using independent samples $t$ tests among dichotomous subgroups (e.g. gender) and one-way ANOVA with Tukey post-hoc analysis among multilevel groups (e.g. MetS components). All tests were considered significant if their $p$ values were below 0.05. Microsoft Excel 2016 was used for data exclusion and arithmetic processing, while statistical tests and graphs were done using IBM SPSS Statistics for Windows, version 20.0 (Armonk, New York: IBM Corporation, released 2011).

Results
Of the 22503 SUA measurements identified by searching the database within the timeframe, 3474 were baseline measurements in normal individuals (Group 1 – patients without comorbid musculoskeletal, cardiovascular, kidney and cancer diseases), of which 34.3% came from men ($n = 1191$) and 65.7% came from women ($n = 2283$). The ICD-10 coding for these individuals revealed non-specific joint complaints (for example back pain, work-related musculoskeletal complaints, fibromyalgia, screening etc.) and primary osteoarthritis. Of these 3474 SUA measurements, 3318 were retained in the analysis of RI after eliminating outliers (Group 2) as described in the Methods section (Figure 1), of which 33.3% came from men ($n = 1105$) and 66.7% came from women ($n = 2213$), giving a 2.0 ratio of women to men.
Of the total search results, 11132 SUA measurements came from individuals without comorbid
musculoskeletal, kidney and cancer diseases but with at least one MetS component (Group 3), of which 24.5% came from men (n = 2725) and 75.5% came from women (n = 8407). As expected in all groups, mean SUA levels were significantly higher in men compared to women (Table 1). On average, women were significantly older than men.

Least square analysis of Group 2 revealed the following SUA RI: 3.43-6.19 mg/dL for the entire sample, 4.44-7.01 mg/dL for men, and 3.28-5.56 mg/dL for women, as shown in Figure 2. In Group 1 (n = 3474), 481 normal subjects (13.8% of total) had hyperuricemia according to the manufacturer’s gender-specific ULN values, namely 290 of the 2283 women (12.7% of women) and 191 of the 1191 men (16.0% of men). Applying the ULN which we derived from the least square analysis of Group 2, the proportions of hyperuricemia in Group 1 (n = 3474) increased: 692 normal subjects (19.9% of total), namely 467 of the 2283 women (20.5% of women) and 225 of the 1191 men (18.9% of men; Figure 3). In Group 3, mean SUA levels increased with the number of MetS components and there was a statistically significant difference between means of

Table 1. Age and serum uric acid (SUA) in the selected samples

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>SUA (mg/dL)</th>
<th>66th%ile (mg/dL)</th>
<th>75th%ile (mg/dL)</th>
<th>ULN (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=3474)</td>
<td>56.9 (14.1)</td>
<td>4.94 (1.59)</td>
<td>6.10</td>
<td>6.40</td>
<td>-</td>
</tr>
<tr>
<td>Men (n=1191)</td>
<td>56.0 (15.5)</td>
<td>5.74 (1.54)</td>
<td>6.30</td>
<td>6.70</td>
<td>-</td>
</tr>
<tr>
<td>Women (n=2283)</td>
<td>57.5 (13.3)*</td>
<td>4.52 (1.44)*</td>
<td>4.90</td>
<td>5.30</td>
<td>-</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=3318)</td>
<td>57.1 (13.7)</td>
<td>4.81 (1.35)</td>
<td>5.36</td>
<td>5.73</td>
<td>6.19</td>
</tr>
<tr>
<td>Men (n=1105)</td>
<td>56.3 (15.4)</td>
<td>5.49 (1.26)</td>
<td>6.10</td>
<td>6.40</td>
<td>7.01</td>
</tr>
<tr>
<td>Women (n=2213)</td>
<td>57.6 (12.7)*</td>
<td>4.46 (1.25)*</td>
<td>4.90</td>
<td>5.28</td>
<td>5.56</td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=11132)</td>
<td>61.3 (12.2)</td>
<td>4.91 (1.51)</td>
<td>5.42</td>
<td>5.86</td>
<td>-</td>
</tr>
<tr>
<td>Men (n=2725)</td>
<td>58.9 (13.9)</td>
<td>5.52 (1.37)</td>
<td>6.10</td>
<td>6.43</td>
<td>-</td>
</tr>
<tr>
<td>Women (n=8407)</td>
<td>61.9 (11.5)*</td>
<td>4.69 (1.50)*</td>
<td>5.20</td>
<td>5.60</td>
<td>-</td>
</tr>
</tbody>
</table>

Notes: see Methods section for definition of Groups; age and SUA are reported as “mean (standard deviation)”; percentiles (%ile) are reported only for SUA; gender differences were assessed by two-tailed independent samples t tests: * p = 0.003, # p < 0.0001, & p = 0.027; upper limit of normal (ULN) was generated for Group 2 with least square analysis according to Methods section.
SUA among subgroups of MetS components as determined by one-way ANOVA, both in men (F(3, 2861) = 3.9; p = 0.009) and in women (F(3, 8403) = 45.1; p < 0.001). Post-hoc analyses of these ANOVA tests are reported in Figure 4.

Discussion

The results of this study are summarized in Table 1, which report relevant and useful cut-offs beyond which hyperuricemia can be defined in this sample and carefully extrapolated to the general population (similar efforts were done for haemoglobin [23], serum calcium and magnesium [24]). In the literature, population-based SUA RIs and ULNs are relatively sparse and vary considerably: for example, 2.6-8.2 mg/dL in an Indian population sample [25] or 3.01-7.75 mg/dL in men and 2.19-7.45 mg/dL in women in a healthy Chinese geriatric sample [26]. Regarding mean SUA levels, they seem to be ele-
vated in Western countries: for example, in Italy only 17.6% of controls had SUA below 6 mg/dL [27], while in the United States, NHANES I data showed mean SUA of 5.5 mg/dL in all, 6.22 mg/dL in men and 4.89 mg/dL in women [3]. The only available data of mean SUA in a large sample of Romanians come from SEPHAR II [28], which screened 1975 subjects presenting to their general practitioners. The authors used the central laboratory RI for SUA (2.40-5.70 mg/dL for women and 3.4-7.0 mg/dL for men) and reported an overall SUA mean of 4.93 (1.42) mg/dL, a figure very similar to ours.

The definition of hyperuricemia using ULN cut-offs is highly variable in the literature [29] and it ranges from 6 or 7 mg/dL irrespective of gender [27], to 7.7 mg/dL in men [30] and 5.7 mg/dL [31] to 6.6 mg/dL in women [30]. This variability could be partly explained by inherent influencing factors (e.g. sample selection method, time of measurement, age, gender, race, adiposity, diet, consumption of alcohol and tobacco etc.) and choice of measuring principle. However, it also highlights the underlying issue associated with defining disease based on dichotomous ruling, when consensus is lacking. Like all biological processes, purine metabolism and consequently uricemia are continuous phenomena: categorizing them based on a single threshold, although practical, is not truly representative. Importantly, cases in the vicinity of the cut-off will risk being misclassified as either false positives or false negatives.

In order to avoid laboratory variability, there have been attempts to define hyperuricemia using a statistical approach and thus creating a universal cut-off: 2 SD above the laboratory mean of healthy individuals [32] (in our sample it would result in a ULN of 8 mg/dL for men and 7 mg/dL for women). Since most reported means of SUA revolve around 6 mg/dL and since the SD is expected to be around 1 mg/dL, this approach does not ultimately resolve the issue and it may actually result in less diagnosed cases of hyperuricemia in some laboratories and populations. Another statistical approach was to define

Figure 4. Mean serum uric acid (SUA) according to gender and number of metabolic syndrome components (none or any 1, 2 or 3-4 from obesity, arterial hypertension, type 2 diabetes mellitus and dyslipidemia). P values represent the significance of post-hoc Tukey comparisons of significant one-way ANOVA tests per gender
hyperuricemia above the gender-specific 75% percentile of SUA measurements [33] (which would give in our Group 2 a ULN of 6.4 mg/dL for men and 5.3 mg/dL for women). Defining hyperuricemia simply based on the third quartile, despite it violating the rigors of statistical data distribution, has particular advantages in the case of SUA. First, real (unprocessed) datasets of SUA measurement are most likely not normally distributed (from what we observed, they have a tendency to be skewed toward the ULN/maximum, maybe because of the so called cases of “asymptomatic hyperuricemia” or selection bias). Using the third quartile as ULN unsophisticatedly removes upper outliers and it produces ULN values closer to the epidemiological thresholds of pathologic cardiovascular and metabolic associations of SUA. More sophisticated statistical methods for deriving RI and ULN, as the one we used, make the assumption that SUA measurements are normally distributed and that all the relevant values reside within 2 SD either side of the mean (encompassing roughly 95% of data). Deriving RIs and ULNs requires the selection of a core set of data which may actually falsify the underlying SUA distribution in the original population.

A totally different approach to defining hyperuricemia is to take into account in vivo biochemical behaviour of MSU. In this sense, a solubility saturation cut-off was proposed to define hyperuricemia: MSU reaches its maximal concentration equilibrium in vitro at 6.8 mg/dL SUA at 37°C and at 6.0 mg/dL SUA at 35°C [9, 34]. Theoretically in vivo, MSU crystals tend to deposit in tissues beyond a similar level of MSU maximal concentration equilibrium, assuming a simplified composition of intravascular, interstitial and synovial fluids. This definition method disregards gender and is closer to the actual physical phenomenon of MSU presence in vivo, but is limited by its theoretical background: MSU deposition is characteristic to gout, therefore biochemically-defined cases of hyperuricemia in fact assess the risk of gouty arthritis and stone formation or kidney damage, disregarding epidemiologic evidence of cardiovascular and metabolic effects, which do not seem to be mediated by tissue MSU deposition. Guidelines issued by international rheumatology organizations (e.g. [35]) regarding the management of hyperuricemia in gout emphasize the importance of treating to target. Clinicians are strongly encouraged to maintain patients’ SUA levels below 6 mg/dL, the reasons behind this recommendation being tophi dissolution and epidemiological evidence of lower flare risk. Considering our results, we could further develop this deterministic chain and assert that uric acid deposits dissolve and gout remits when SUA is below 6 mg/dL because this level is normal. The normality of this therapeutically-achieved SUA level may cause the observed beneficial effects, a relationship which is similar to blood pressure, atherosclerosis and cardiovascular events. Of course, normalizing SUA does not cure gout, it only deprives it of its main pathogenic mechanism, which should theoretically impact other gout-associated morbidity, such as cardiovascular disease.

In fact, the only reason we are discussing the ULN of SUA is the often-cited observation of morbidity and mortality associated with high-normal SUA. Further causal meta-analytical evidence is provided by reports that allopurinol, a SUA lowering drug, improves endothelial dysfunction [36], arterial stiffness [37] and blood pressure [38]. However, contradicting literature exists: the association of SUA with cardiovascular mortality was unconvincing in an umbrella review of meta-analyses [39]; it becomes insignificant if kidney function is accounted for [40]; SUA levels above 8 mg/dL non-significantly increase mortality of men and are not associated with mortality in women [41]; SUA was not an independent predictor of cardiovascular and CHD mortality [42]. This information may not
contradict the majority of reports if both SUA elevation and cardiovascular risk are being raised by a common cause, a preceding metabolic disorder to which intervention studies hint: normalizing SUA with allopurinol does not significantly decrease serum lipids [43], but some lipid lowering drugs also lower SUA [44]. Supporting this metabolic disorder hypothesis, our results show a significant trend of SUA increase with additional MetS components, suggesting that hyperuricemia is just another manifestation of the pathologic process which leads to cardiovascular risk. Since the above-cited contradictory reports do not deny any involvement of SUA in metabolic and cardiovascular morbidity and mortality, the need for outcome-defined ULN of SUA becomes clear. In this sense, Desideri et al. [45] are already investigating this issue in an Italian population. These types of study design applied in multiple populations should offer final arguments for outcome-defined ULN of SUA and should provide a basis for an international consensus of experts on the matter. By analysing our results as reported in Table 1 and Figure 2, it seems that the best way to define hyperuricemia is by using the gender-specific 66th percentile of data range.

However, our study of ULN values could have been influenced by a number of limitations and confounders which we were unable to control by design: human measurement error (minimized by enrolling a single biochemist), machine and SUA kit variability (minimized by calibrations according to manufacturer’s indications), lack of information regarding specific behaviour of subjects (e.g. smoking, diet), selection bias (single tertiary medical centre specialized in rheumatology), diagnoses bias (unrecognized, undeclared or subclinical disease, insufficient or incorrect ICD-10 coding by each attending physician), methodology bias (e.g. outlier elimination, least square analysis, Hoffman method). The large sample size may have cancelled the effect of some limitations, but most likely confounding factors remained an issue in the data.

**Conclusion**

Defining hyperuricemia by its ULN from laboratory-derived RIs is inappropriate due to epidemiologic evidence of MetS (also illustrated by our data) and cardiovascular risks. Instead, we suggest hyperuricemia should be defined using a statistical approach of upper decision limit selection (corresponding to the gender-and-population-specific 66th percentile of data range) upon which an international consensus should exist as an expression of evidence and expert opinion. Unfortunately, ideal SUA levels seem to have disappeared in Western societies most probably due to modern diet and increasing prevalence of MetS.

**Abbreviations**

AHT - arterial hypertension  
CCRD - “Ion Stoia” Clinical Centre for Rheumatic Diseases  
CHD - coronary heart disease  
ICD - International Statistical Classification of Diseases and Related Health Problems  
MetS - metabolic syndrome  
MSU - monosodium urate  
RI - reference intervals  
SD - standard deviation  
SUA - serum uric acid  
T2DM - type 2 diabetes mellitus  
ULT - urate-lowering therapy  
ULN - upper limit of normal

**Authors’ contribution**

CC (Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing)  
HP (Conceptualization; Investigation; Method-
ology; Project administration; Resources; Software; Supervision; Validation; Writing – review & editing)

ER (Conceptualization; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Writing – review & editing)

CDM (Conceptualization; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Writing – review & editing)

IG (Conceptualization; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Writing – review & editing)

CCP (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Writing – original draft; Writing – review & editing)

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Conflicts of interest

None declared.

References


