Seasonal shifts and population characteristics of uric acid in eastern coastal China: a big data analysis from Hangzhou

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Abstract

Objective

Uric acid (UA), the end-product of purine metabolism, is linked to various medical conditions such as gout and cardiovascular diseases. The increasing incidence of hyperuricaemia and gout in China highlights the need to establish accurate reference intervals for UA. This study uses data from a real-world population to examine the distribution of UA levels across various demographic groups, with a specific focus on seasonal variations in UA concentrations. Through the application of an indirect statistical method, the research aims to establish more precise UA reference intervals for clinical use.

Methods

We analysed 749,739 serum UA data from adults (≥18 years) over 2 years, 2021-2022, studying seasonal, gender, and age effects. The reference intervals were established via the indirect method, and the differences from the manufacturer's ranges were assessed using the reference change value (RCV).

Results

UA levels showed seasonal variations with significant gender disparities. In winter/spring, males 18–44: 262–539 µmol/L, females: 175–385 µmol/L; males 45+: 243-525 µmol/L, females: 185–406 µmol/L. In summer/autumn, males 18–44: 273–552 µmol/L, females: 185–395 µmol/L; males 45+: 250–537 µmol/L, females: 192–410 µmol/L.
A significant difference was observed in the reference range for males compared to the manufacturer's range, but no difference for females.

Conclusion

Extensive data analysis has uncovered seasonal fluctuations and notable gender- and age-related effects on serum UA concentrations. Using the indirect method to establish more refined reference intervals for serum UA levels confers practical relevance in clinical practice.

Key words

uric acid, reference values, real-world data, seasonal variation

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Received on February 1, 2025; accepted in revised form on May 5, 2025.

Competing interests: none declared.

Introduction

Uric acid (UA) is the final product of purine metabolism, primarily produced through the degradation of nucleic acids and other purine compounds (1). The level of UA is determined by the dynamic balance between endogenous purine degradation and renal excretion. An increase in UA production or a decrease in its excretion can elevate serum UA concentrations, leading to hyperuricaemia. Hyperuricaemia, which can be primary or secondary, poses significant risks for gout, kidney disease, hypertension, peripheral vascular disease, diabetes, and coronary heart disease (2-4). Therefore, monitoring UA levels in individuals is essential to mitigate these health risks. In recent years, due to the rapid development of the Chinese economy and changes in dietary patterns, the incidence of hyperuricaemia and gout has increased annually, particularly among younger individuals. Research has demonstrated that factors such as gender, age, dietary structure, and season significantly impact UA levels in the population (5, 6). Additionally, different regions exhibit varying rates of gout incidence. Therefore, investigating UA levels in real-world populations, identifying relevant factors, and understanding the characteristics of UA changes are essential for managing hyperuricaemia effectively.

During our work at the hospital, we observed an increase in the number of individuals with hyperuricaemia during the summer and autumn compared to winter and spring. Previous research by Romaszko *et al*. indicated a correlation between UA levels and seasonal factors in the population (7); however, these relationships were not statistically significant and require further exploration. Therefore, we aim to utilise big data statistical analysis to verify whether there are seasonal differences in UA levels in Hangzhou, China.

Utilising reference intervals is crucial in evaluating whether UA levels differ across seasons. However, the current reference intervals used in laboratories do not account for many factors that influence UA concentration and lack subgroup specificity. Additionally, most reference intervals are derived from reagent kit instructions based on the population of the manufacturer's country, which may not apply to other regions. This discrepancy can lead to confusion and misinterpretation in clinical settings. In this study, we analysed the distribution of UA levels across different seasons, genders, and age groups in the population of Hangzhou, China, from January 2021 to December 2022 (8). Following the EP28-A3c guidelines (9-11), we identified key influencing factors through indirect methods and successfully established more detailed reference intervals for clinical reference, aiming to enhance the accuracy and reliability of clinical diagnoses.

Materials and methods

Study subjects

This real-world study is based on serum UA test data from hospitalised patients, outpatients, and individuals undergoing health examinations at our hospital between January 2021 and December 2022. After excluding data with missing information and duplicates, the study included clinical laboratory data from a total of 749,739 subjects. This study was approved by the Research Ethics Committees of Zhejiang Provincial People's Hospital (QT2023382).

Laboratory measurements

Blood samples from outpatients were collected during routine clinic visits throughout the day. For inpatients, blood samples were primarily collected in the early morning, typically between 6:00 am and 8:00 am. For individuals undergoing health examinations, blood samples were collected during scheduled appointments, usually in the morning. All samples were prepared, collected, transported, and processed according to the guidelines for sample collection and transportation (PUMCHL-L-2-Q25b-04). Before testing, the samples were centrifuged at 3000 rpm for 5 minutes to separate the serum from the samples. The UA reagent (OSR6298, Beckman Coulter Laboratory Systems Co., Ltd.), calibration material (66300, Beckman Coulter Ireland Inc.), and quality control materials (657365, Beckman Coulter, Inc., USA) were used according to the

manufacturer's instructions. UA levels were measured using the AU5800 automatic biochemical analyser (Beckman Coulter, Inc., USA). The uricase-peroxidase method was employed for detection. The instrument undergoes annual calibration and maintenance and participates in the annual proficiency testing organised by the National Clinical Laboratory Center. Test procedures are executed according to standard operating procedures, with strict internal quality control measures implemented before analysis to monitor the accuracy of the instruments. These steps ensure the veracity and reliability of the test results. After testing, all data were stored in a database for future analysis.

Data processing and analysis

- Statistical analysis

Excel 2007 (Microsoft, Redmond, WA, USA) was used for data storage, basic processing, and calculations. Statistical analyses were conducted using SPSS v. 26.0 (IBM Inc., Armonk, NY, USA).

- Normality test of data

Histograms and frequency tables were used to plot the data distribution. The Kolmogorov-Smirnov (D-test) was used to test the normality of the research data. If $p>0.05$, the data is normally distributed; If $p<0.05$, it is non-normally distributed.

- Outlier removal

Box plots and stem-and-leaf plots were employed to eliminate outliers from the experimental data included in this study. The subsequent analysis was conducted on the remaining data.

- Data analysis and reference interval establishment

The median of the serum UA testing data for each day from January 2021 to December 2022 was calculated to observe the seasonal variations of UA. Seasons were categorised as follows: Spring (March to May), Summer (June to August), Autumn (September to November), and Winter (December to February) (12). Adult physical examination data from 2022 were selected to analyse differences in UA levels among different groups based on gender, age, and season. The independent samples Mann-Whitney U-test was used to compare differences between groups based on gender. The Kruskal-Wallis test was used to analyse the effects of age and season on UA levels. Normally distributed continuous data were expressed as mean and standard deviation (SD) and the 95% reference range was calculated as (mean±1.96SD). Non-normally distributed continuous data were expressed as Median (P25, P75), and the non-parametric method [median (P2.5, P97.5)] was used to establish the reference range (9).

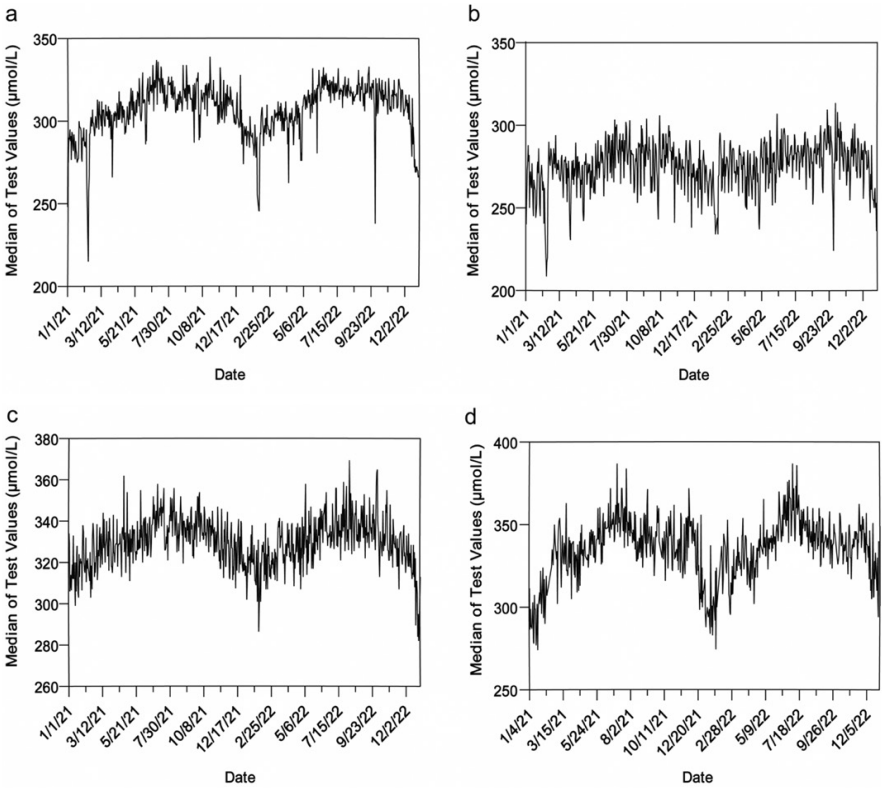

Fig. 1. Daily median change of UA level in the population from January 2021 to December 2022. **a**. overall population; **b**. inpatient population; **c.** outpatient population; **d**. physical examination population.

- Comparison of reference intervals

In contrast to the direct approach involving rigorous screening of healthy volunteers for dedicated testing, we adopted an indirect method by utilising pre-existing clinical laboratory data – typically comprising mixed datasets of both healthy and non-healthy individuals – to establish local UA reference intervals through statistical identification and extraction of test values approximating healthier subpopulations. The reference change value (RCV) assessed the differences between the indirect method and the reference intervals provided by the manufacturer.

RCV calculation formula: $RCV = 2 \times Z \times (CVa2 + CVi2)1/2 \times 100\%$, where CVa is the analytical coefficient of variation, CVi is the within-subject biological coefficient of variation, and Z is the chosen significance probability.

The relationship between RCV and the lower limit (RCVmin) and upper limit (RCVmax) of the reference change value of the same group was compared: If both RCVmin and RCVmax were smaller than RCV, there was no statistically significant difference between the reference intervals. If the calculated value of RCVmin or RCVmax was larger than RCV, there was a statistically significant difference between the reference intervals.

Results

Data distribution

A total of 749,739 subjects were included from January 2021 to December 2022. Among them, there were 405,418 males with a median age of 55 years (range: 39–67 years) and a median UA

level of 350 μmol/L (range: 277–419 μmol/L). There were 344,321 females with a median age of 51 years (range: 36–64 years) and a median UA level of 273 μmol/L (range: 223–328 μmol/L).

Trends in UA concentration changes

Based on our data analysis from January 2021 to December 2022, seasonal variations in UA levels were observed across the general population, hospitalised patients, outpatients, and physical examination groups (Fig. 1). The median UA levels exhibited an upward trend in the summer and a downward trend in the winter, suggesting this pattern may represent a general trend, with UA levels rising during the summer and decreasing during the winter. These seasonal changes were significant in the general population, outpatient, and physical examination groups, but not in the hospitalised group. The absence of a clear trend among hospitalised patients is likely attributable to several factors. Hospitalised patients often experience fluctuations in UA levels due to underlying diseases and the effects of various medications. Additionally, their diet and fluid intake are typically strictly controlled and kept stable, including reduced consumption of purine-rich and high-purine foods (13). Combined with prolonged hospitalisation, these factors may further reduce the impact of seasonal changes, dietary factors, and activity levels on UA concentrations.

Establishment of the reference range

When establishing reference intervals for UA levels, ensuring the objectivity and comparability of the data is of paramount importance. Given that the UA levels in hospitalised populations may be influenced by a variety of diseases and therapeutic interventions, these factors could introduce biases that compromise the accuracy of UA levels. Therefore, to obtain a more accurate reference interval, we elected to exclude these potential confounding factors. We utilised the UA level data from the 2022 annual health examination cohort as the foundation for establishing the reference interval. This decision was based on several critical considerations: firstly, individuals undergoing health examinations are generally healthier, and thus their UA levels better reflect physiological variations in the absence of disease. Secondly, by confining data collection to a single year, we effectively eliminated variations in testing technologies and quality control measures that could arise over time, ensuring the consistency and comparability of the data. Furthermore, due to the sufficiently large sample size, we were able to derive a highly credible reference interval through statistical analysis, providing more reliable guidance for clinical practice.

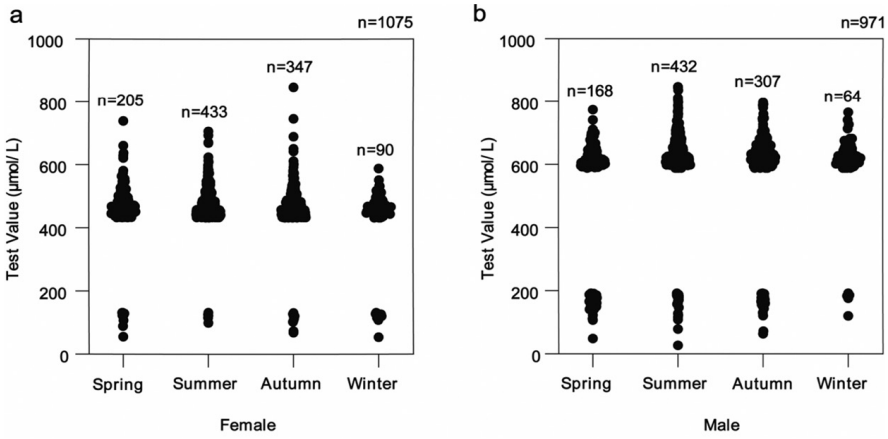

Fig. 2. Distribution of excluded outliers. **a**. Female; **b**. Male

Outlier exclusion

A total of 89,223 adult physical examination data from 2022 were selected, including 49,392 males and 39,831 females. The data were subjected to outlier exclusion using box plots and stem-and-leaf plots. After exclusion, a total of 87,177 data points were obtained, including 48,421 males and 38,756 females (Supplementary Table S1). The distribution of excluded outliers was as follows: among males, there were 168 individuals in spring, 432 individuals in summer, 307 individuals in autumn, and 64 individuals in winter. Among females, there were 205 individuals in spring, 433 individuals in summer, 347 individuals in autumn, and 90 individuals in winter (Fig. 2). After exclusion, the data showed a non-normal distribution (D-test $p<0.05$), and the frequency distribution showed a skewed and peaked distribution.

Analysis of reference intervals between different seasons

The Kruskal-Wallis H test was employed to discern potential variations in UA reference intervals across different seasons. The findings of our study indicate that there are significant differences in UA levels across different seasons ($p<0.001$). It is noteworthy that significant differences were observed in pairwise comparisons between all seasons: spring, summer, autumn, and winter (Suppl. Table S2):

$Z_{\text{winter \& spring}} = 11.035, p<0.001$;
$Z_{\text{winter \& autumn}} = 18.789, p<0.001$;
$Z_{\text{winter \& summer}} = 28.324, p<0.001$;
$Z_{\text{spring \& autumn}} = -8.189, p<0.001$;
$Z_{\text{spring \& summer}} = -19.776, p<0.001$;
$Z_{\text{autumn \& summer}} = 13.662, p<0.001$)

Following a comparative analysis of the seasonal groupings, reference intervals were consolidated for spring and winter, as well as for summer and autumn, to account for the observed similarities in UA levels (Table I). This approach ensures that the reference intervals more accurately reflect the natural physiological fluctuations associated with seasonal changes.

Analysis of reference intervals between different genders

Mann-Whitney U-test revealed a statistically significant difference in UA levels between males and females (Suppl. Table S3, $Z= -195.522, p<0.001$). Consequently, gender-specific biological reference intervals were established to reflect the observed disparities in UA levels in the Hangzhou population.

Table I. Reference intervals of UA after seasonal consolidation (μmol/L).

Groups	18–44 years		≥45 years	
	Male	Female	Male	Female
Spring & Winter	262~539	175~385	243~525	185~406
Summer & Autumn	273~552	185~395	250~537	192~410

Analysis of reference intervals between different age groups

Our statistical analysis reveals discernible differences in UA levels across various age groups, with distinct patterns emerging between genders. Supplementary Figure S1 presents a correlational graph depicting the interplay among UA concentrations, gender, and age based on 87,177 data observations. Among males, UA levels exhibit a gradual decline with advancing age, whereas in females, there is a consistent upward trend in these levels as age progresses.

Participants were categorised into three age groups: 18–44 years, 45–60 years, and >60 years. The Kruskal-Wallis H test was employed to compare the reference intervals across different groups, and the results revealed statistically significant differences within the age groups ($p<0.001$). Subsequent pairwise comparisons demonstrated variations in UA levels between the 18–44 years group and both the 45–60 years group and the >60 years group ($Z= -6.292$, $p<0.001$; $Z= -6.701$, $p<0.001$). However, there was no significant difference in UA levels between the 45–60 years group and the >60 years group ($Z= -1.483$, $p=0.138$). Hence, for subsequent statistical analyses, the age groups of 45–60 years and over 60 years were merged. Based on the aforementioned statistical analysis, we have established distinct biological reference intervals stratified by gender, age, and season (Suppl. Table S4).

Comparison of indirect method reference ranges with manufacturer reference intervals

The laboratory's cumulative index of variation (CVa) for UA is recorded at 1.49%, whereas the within-subject biological coefficient of variation (CVi) is 8.6% (data source: Westgard website). The RCV value is calculated to be 24.19%. Table II presents a comparative analysis of the reference intervals established using the indirect method and the reference ranges provided by the manufacturer, which in their documentation, only offer distinct intervals for different genders. In the male cohort, with the exception of the winter-spring group for males aged ≥45 years, there were statistically significant differences in the reference intervals when compared to the manufacturer's reference intervals for all other groups. The upper limits of the reference intervals established using the indirect method for males were consistently higher than those set by the manufacturer. Within the female cohort, the RCVmin and RCVmax values for each group were both lower than the RCV values, and no statistically significant differences were observed when compared to the manufacturer's reference intervals.

Discussion

Real-world research entails collecting patient data in real-world settings and obtaining valuable information through big data analysis. Laboratory test data is one of the crucial sources. In this study, we conducted a large-scale data analysis of UA levels in the Hangzhou population to explore the distribution patterns of UA levels in the real world. After identifying the influencing factors, we established targeted reference intervals to accurately assess the population's UA levels.

Our analysis revealed seasonal variations of UA levels in the Hangzhou population from 2021 to 2022. The analysis revealed a significant increase in UA levels among the general population, outpatients, and individuals undergoing physical examinations during the summer months, with a corresponding significant decrease observed in the winter season. We propose that the observed seasonal variations in UA levels may be attributed to fluctuations in ambient temperature. Elevated temperatures are associated with the production of more concentrated urine and a subsequent reduction in urine output (14, 15), which in turn can lead to a diminished excretion of UA and a consequent rise in blood concentration. Furthermore, the correlation between UA levels and seasonal changes could also be significantly influenced by regional dietary patterns and lifestyle habits. Hangzhou features a subtropical monsoon climate with distinct seasons,characterised by hot, humid summers and mild, moist winters. Under such climatic conditions,during the high-temperature periods in summer, residents are likely to increase their intake of cold drinks and beer. These

Table II. Comparison of indirect method reference ranges with manufacturer reference ranges (μmol/L).

Groups	Manufacturer reference ranges	Indirect method reference ranges	RCV_{min}(%)	RCV_{max}(%)	RCV (%)
Male 18–44 years, Winter & Spring	208~428	262~539	25.96	25.93	
Male 18–44 years, Autumn & Summer	208~428	273~552	31.25	28.97	
Male ≥45 years, Winter & Spring	208~428	243~525	16.83	22.66	
Male ≥45 years, Autumn & Summer	208~428	250~537	20.19	25.47	24.19
Female 18–44 years, Winter & Spring	155v357	175~385	12.90	7.84	
Female 18–44 years, Autumn & Summer	155~357	185~395	19.35	10.64	
Female ≥45 years, Winter & Spring	155~357	185~406	19.35	13.73	
Female ≥45 years, Autumn & Summer	155~357	192~410	23.87	14.85	

beverages may indirectly affect uric acid levels. Moreover, the cohort under analysis resided in coastal regions rich in seafood, and exhibited a higher consumption of purine- and protein-rich foods during the summer, potentially contributing to increased production of purine metabolites and a subsequent elevation in UA levels. Thus, our extensive data analysis demonstrates that, in actuality, the population's UA levels undergo seasonal variations rather than maintaining a stable and uniform concentration. This observation is of considerable importance for the holistic assessment of UA levels across the population.

Consistent with prior studies, our research also found differences in UA levels between genders. Males displayed higher median UA levels (350 μmol/L, range: 277–419 μmol/L) than females (273 μmol/L, range: 223–328 μmol/L). Additionally, males exhibited gradual decreases in UA levels with age, while females demonstrated increases. The differences in UA concentration levels and age-related changes between males and females may be due to oestrogen in females, which can promote UA excretion (16, 17), while testosterone in males can promote UA reabsorption in the kidneys and inhibit its excretion.

Owing to the absence of specific national or regional benchmarks for UA levels, Chinese laboratories often defer to reference intervals established by manufacturers, which are predominantly informed by data from European and American populations. Therefore, in this study, adhering to the EP28-A3c guidelines jointly issued by the American Association for Clinical Chemistry and the International Federation of Clinical Chemistry, UA reference intervals for the Hangzhou population were established, considering gender, age, and season. Owing to the non-normal distribution in the data, non-parametric methods were used, setting the 2.5^{th} and 97.5^{th} percentiles as the lower and upper limits of the reference range, respectively (9).

Upon analysis of the reference interval data that we established, it became evident that while there was a pronounced seasonal variation in serum UA levels within the population, this fluctuation did not yield a statistically significant difference in the reference interval values. This finding may be attributed to the exclusion of outliers. Specifically, during the winter and spring seasons, 232 males were excluded, whereas in the summer and autumn seasons, 739 males were excluded. Among females, 295 were excluded in the winter and spring, and 780 in the summer and autumn. It is noteworthy that a significantly higher number of outliers were excluded during the summer months compared to winter. Furthermore, as depicted in Figure 2, the majority of the excluded outliers represented high values, which in turn diminished the variability observed in the reference intervals.

We conducted a subsequent analysis to compare the reference intervals ascertained via the indirect method with those proffered by the manufacturer. As previously noted, except for the reference intervals for the demographic of males aged forty-five years and above during the winter and spring seasons, the serum UA concentrations for all other male cohorts typically surpassed the reference intervals as stipulated by the manufacturer, demonstrating statistically significant discrepancies between these two sets of data. In contrast, within the female cohort, the reference interval values, while nominally elevated, did not manifest a statistically significant divergence. Consequently, there is a compelling need to develop reference intervals for UA levels that are calibrated to the population-specific distribution characteristics of UA levels. This tailored approach is essential for the enhancement of precision in the assessment of individual UA levels.

Based on the seasonal variations in serum uric acid levels, clinical practitioners may implement corresponding pharmacological adjustments. For patients diagnosed with hyperuricaemia or gout, physicians could consider titrating upward the dosage or administration frequency of urate-lowering medications during summer and autumn to optimise serum urate control and mitigate the risk of gout flares. In cases of recurrent seasonal exacerbations, prophylactic low-dose medication initiation prior to seasonal transitions may be warranted for high-risk patients with prior gout history to achieve therapeutic urate-lowering effects and prevent acute attacks. When modifying therapeutic regimens, rigorous monitoring of hepatic and renal function parameters is imperative, necessitating personalised dose adjustments based on comprehensive patient evaluation. Complementary nutritional interventions should be concurrently implemented. Dietary modifications during summer and autumn should emphasise alcohol abstinence and restriction of sugar-sweetened beverages. Clinical recommendations may include adequate hydration maintenance and consumption of low-purine dietary sources to synergistically enhance therapeutic outcomes.

Admittedly, there are several limitations to this study. The reference intervals established herein were predicated on the Beckman AU detection system, necessitating subsequent validation to ascertain their applicability across diverse detection systems. Furthermore, the variability in outlier exclusion methodologies within the indirect method could result in the removal of disparate data quantities, which may exert an influence on the outcomes. Hence, the implementation of a direct method for the determination of reference ranges may be warranted if deemed necessary.

Conclusion

Through the big data analysis of the UA level of the population in Hangzhou, our study reveals that the UA level of the population is affected by obvious seasonal fluctuations. Additionally, we observed significant variations in UA levels across different genders and age groups. By applying the indirect method, we successfully established the reference intervals of UA suitable for different seasons and different populations, thus providing a more accurate reference standard for clinical evaluation. These findings underscore the importance of considering seasonal and demographic influences when assessing UA levels in clinical practice.

Practical application

This article has established a more refined reference range for UA, tak-

ing into account seasonal variations as well as gender and age factors, thereby providing the clinical field with a more precise diagnostic tool. This stratification is expected to enhance the sensitivity of UA testing, assisting clinicians in the accurate identification and management of hyperuricaemia, and facilitating the adjustment of medication dosages and the assessment of therapeutic efficacy. Furthermore, personalised UA management strategies could reduce the risk of gout attacks in populations and optimise treatment regimens. Concurrently, recognising seasonal fluctuations allows for targeted lifestyle and dietary recommendations for patients, and in the realm of public health, it enables the strengthening of gout education and preventive measures during high-risk seasons.

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