

Serum Creatinine Reference Interval and Discordance with Manufacturer-Supplied Limits in Apparently Healthy Mauritanian Adult Male Blood Donors: A Cross-Sectional Study

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Abstract

Background

Serum creatinine is widely used to assess kidney function, but its interpretation depends on population characteristics and analytical methodology. Locally applicable reference intervals remain poorly characterized in Mauritania. This study aimed to derive a candidate serum creatinine reference interval in apparently healthy Mauritanian adult male blood donors and to assess discordance with the manufacturer-supplied reference limits.

Methods

This single-centre cross-sectional study included 288 adult blood donors recruited at the National Blood Transfusion Centre in Nouakchott between May and November 2024. Serum creatinine was measured using an IDMS-traceable compensated Jaffé assay on a BioSystems A15 analyser. The central 95% reference interval was estimated non-parametrically according to CLSI EP28-A3c, with 90% confidence intervals for the reference limits obtained by bootstrap resampling. Because only 16 participants were women, the primary reference-interval analysis was restricted to men ($n = 272$). Discordance with the manufacturer-supplied male interval of 7.0–12.0 mg/L was quantified, and associations with age and body mass index were explored.

Results

Among men, the candidate serum creatinine reference interval was 6.50–15.10 mg/L (0.65–1.51 mg/dL; 57–134 $\mu\text{mol/L}$). The 90% confidence intervals were 5.55–7.25 mg/L for the lower reference limit and 14.20–15.55 mg/L for the upper reference limit. Sixty-one men (22.4%) had creatinine concentrations outside the manufacturer-supplied interval, including 52 (19.1%) above its upper limit. Increasing body mass index was associated with a higher prevalence of discordance with the manufacturer interval (adjusted prevalence ratio 1.58 per 5 kg/m², 95% CI 1.09–2.31), whereas age was not independently associated with discordance.

Conclusions

The serum creatinine reference interval observed in apparently healthy Mauritanian adult male blood donors was wider than the manufacturer-supplied interval, and more than one in five men were classified outside the latter. These findings support local verification of manufacturer-supplied creatinine reference limits. The proposed interval should be considered method-specific and requires independent validation before routine clinical implementation.

Background

Serum creatinine remains one of the most widely used laboratory markers of kidney function and is central to estimated glomerular filtration rate (eGFR), chronic kidney disease assessment, and drug-dose adjustment [1–3]. However, serum creatinine concentration reflects not only renal clearance but also physiological determinants such as muscle mass, sex, age, and diet [4, 5]. Appropriate interpretation therefore depends on reference limits that are applicable to both the population tested and the analytical method used.

A reference interval represents the central distribution of laboratory results in a defined reference population and is distinct from a clinical decision limit [6, 7]. Its validity depends on reference-population characteristics, pre-analytical conditions, analytical methodology, and calibration [6, 8–12]. Consequently, laboratory guidelines recommend verification or establishment of locally applicable reference intervals rather than uncritical adoption of externally derived values [6, 10–12]. This issue is particularly relevant for serum creatinine because analytical performance remains method dependent, and differences between Jaffé and enzymatic assays may persist despite IDMS traceability and standardization [13–17].

Age- and sex-related differences in serum creatinine reference values have been reported in several adult populations [18–21]. Studies in African populations have reported heterogeneous reference values for serum creatinine and related renal-function markers across countries and settings, in studies differing in population selection, demographic characteristics, and analytical methods [22–29]. Comparable data from Mauritania and neighbouring Sahelian populations remain limited. Mauritanian laboratories may therefore rely on manufacturer-supplied or externally derived limits whose applicability to the local population requires verification.

This study aimed to derive a candidate serum creatinine reference interval in apparently healthy Mauritanian adult male blood donors and to quantify discordance with the manufacturer-supplied reference limits. Secondary analyses examined whether age and body mass index were associated with serum creatinine concentrations or with classification outside the manufacturer-supplied interval. Given the limited availability of locally derived creatinine reference data in Mauritania, the study was intended to provide method-specific evidence to inform local laboratory verification rather than to establish clinical decision thresholds for kidney disease.

Methods

Study design and setting

This single-centre cross-sectional study was conducted at the National Blood Transfusion Centre (Centre National de Transfusion Sanguine, CNTS) in Nouakchott, Mauritania, between 9 May and 26 November 2024. Adult voluntary blood donors were recruited consecutively after being declared eligible for blood donation through routine predonation screening. The study was designed to derive candidate serum

creatinine reference limits using the statistical framework recommended by the Clinical and Laboratory Standards Institute (CLSI) EP28-A3c guideline. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cross-sectional studies.

Study population and eligibility

Eligible participants were adults aged ≥ 18 years who met national blood-donation eligibility criteria following a standardized predonation questionnaire, medical interview, and physical examination. Individuals with self-reported chronic disease, current use of relevant medications, known renal, hepatic, or thyroid disease, or obesity defined as body mass index (BMI) ≥ 30 kg/m² were not eligible.

No additional renal-function investigations were performed specifically for this reference-interval study. Participants were therefore considered apparently healthy rather than confirmed healthy reference individuals.

Inclusion in the analytical dataset required an available serum creatinine measurement together with complete demographic and anthropometric data. Serum creatinine results were available for 288 participants, including 272 men and 16 women. Because the female subgroup was substantially below the minimum sample size recommended for non-parametric reference-interval estimation, the primary candidate reference interval was derived in men.

Before analysis, records were screened for duplicate entries, missing data, anthropometric inconsistencies, and biologically implausible observations. Information on hydration status, recent meat intake, creatine supplementation, and recent strenuous physical activity was not available.

Sample size considerations

No formal hypothesis-testing sample-size calculation was performed because the primary objective was estimation of reference limits rather than testing a predefined exposure–outcome hypothesis. According to CLSI EP28-A3c, at least 120 reference individuals per partition are recommended for non-parametric estimation of a reference interval. This requirement was met for men but not for women. Accordingly, the female subgroup was described for completeness but was not used to establish a reliable sex-specific reference interval.

Anthropometric measurements

Age and sex were recorded at enrolment. Anthropometric measurements were obtained to characterize body size and nutritional status. Body weight was measured using a digital SECA® scale with a precision of 0.1 kg. Height was measured using a portable SECA® stadiometer with a maximum measuring capacity of 2.20 m and a precision of 0.1 cm. BMI was calculated as weight (kg) divided by height

squared (m^2), and the calculated BMI was cross-checked against the value recorded in the study dataset.

Blood sampling and serum creatinine measurement

Fasting was not required before blood donation. Venous blood was collected into plain serum tubes, allowed to clot, centrifuged at 3000 rpm for 10 min, and analysed within 4 h of collection.

Serum creatinine was measured on a BioSystems A15 automated analyser (BioSystems S.A., Barcelona, Spain) using the manufacturer's compensated fixed-time kinetic Jaffé method [30]. Absorbance was measured at 505 nm, and the analyser applied the manufacturer-recommended – 0.30 mg/dL compensation for non-creatinine chromogens. According to the manufacturer's documentation, the assay had a detection limit of 0.04 mg/dL and an analytical measurement range of 0.20–20.0 mg/dL. Manufacturer-reported repeatability coefficients of variation were approximately 3.2% at a creatinine concentration of 1.63 mg/dL and 2.1% at 4.63 mg/dL, with corresponding within-laboratory coefficients of variation of 3.5% and 2.2%, respectively [30].

Creatinine results were recorded in mg/L. Unit conversions used 1 mg/dL = 10 mg/L and 1 mg/dL = 88.4 μ mol/L.

Calibration and internal quality control

A reagent blank was performed daily. Calibration was carried out using the manufacturer-recommended biochemistry calibrator at least every seven days, after reagent-lot changes, or whenever indicated by internal quality-control procedures. Internal quality control was performed using commercial control sera at two concentration levels. Analytical runs that did not meet predefined acceptance criteria were rejected and repeated after appropriate corrective action. According to the manufacturer's assay documentation, calibration of the creatinine method was traceable to an isotope-dilution mass spectrometry (IDMS) reference measurement procedure [30].

Assessment of potential outliers

Potential serum creatinine outliers were assessed using the Tukey method and the Dixon–Reed rule, together with consideration of biological plausibility. Observations were not excluded solely because they fell outside the Tukey $1.5 \times$ interquartile-range fences, and no value was removed solely for the purpose of narrowing the estimated reference interval. The effect of statistically flagged observations on the estimated reference limits was subsequently examined in sensitivity analyses.

Statistical analysis

The distribution of serum creatinine was examined using histograms, kernel-density plots, quantile–quantile plots, box plots, skewness, and kurtosis. The Shapiro–Wilk test was used as supportive information rather than as the sole criterion for assessing distributional characteristics. Continuous variables were summarized using mean $\pm$ standard deviation and median [first quartile–third quartile], as appropriate. Categorical variables were summarized as counts and percentages.

The central 95% serum creatinine reference interval was defined by the 2.5th and 97.5th percentiles and estimated non-parametrically according to the CLSI EP28-A3c statistical framework [6]. Ninety-percent confidence intervals for the lower and upper reference limits were estimated by bootstrap resampling with 10,000 replicates using a prespecified random seed (20260724).

Between-sex differences were examined using the Mann–Whitney U test and Welch's t test. The need for sex-specific partitioning was evaluated using statistical comparisons, effect magnitude relative to the reference-interval width, biological plausibility, and the Harris–Boyd criterion [31]. Differences in serum creatinine across age groups and BMI categories were examined using the Kruskal–Wallis test. Monotonic associations of serum creatinine with age and BMI were evaluated using Spearman rank correlation.

Associations of age, sex, and BMI with mean serum creatinine concentration were further examined using multivariable linear regression with heteroscedasticity-consistent HC3 standard errors. Age was expressed per 10-year increase and BMI per 5 kg/m² increase. Model assessment included examination of residual distributions and influential observations. As a sensitivity analysis, the candidate reference limits were recalculated after exclusion of observations statistically flagged as extreme.

Additional exploratory analyses were restricted to men (n = 272), corresponding to the population in whom the primary candidate reference interval was derived. Modified Poisson regression with a log link and robust sandwich variance was used to estimate prevalence ratios for serum creatinine concentrations outside the manufacturer-supplied male reference interval of 7.0–12.0 mg/L. The binary outcome was therefore defined as serum creatinine < 7.0 mg/L or > 12.0 mg/L. Age and BMI were included simultaneously in the adjusted model.

Quantile regression was additionally used to explore whether associations of age and BMI with serum creatinine differed across the creatinine distribution. Models were fitted at the 50th, 75th, 90th, and 95th percentiles. Confidence intervals were estimated using non-parametric bootstrap resampling with 1000 replicates and a prespecified random seed (20260806). Interpretation of quantile-regression findings was based primarily on bootstrap confidence intervals because asymptotic inference was unstable at some upper quantiles. The locally derived upper reference limit was not used as the primary threshold for binary regression because it was estimated from the same dataset.

All conventional statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using R version 4.3, IBM SPSS Statistics version 26, and RefValAdv version 2.1.

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee of the University of Nouakchott, Mauritania (approval no. 11/23, 4 July 2023; renewed under no. 0004, 19 January 2025). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment. Data were anonymized before statistical analysis.

Use of generative AI-assisted technologies

During manuscript preparation, ChatGPT (OpenAI) was used to assist with language editing, readability, and manuscript formatting. The authors reviewed and edited all resulting text and take full responsibility for the final content.

Results

Study population

The analytical dataset included 288 eligible blood donors with complete serum creatinine, demographic, and anthropometric data. No records were excluded after data-quality checks. Of the 288 participants, 272 (94.4%) were men and 16 (5.6%) were women. Because the female subgroup was too small for reliable non-parametric estimation of a sex-specific reference interval, the primary reference-interval analysis was restricted to the 272 male participants.

The median age of the overall study population was 29.0 years [24.0–36.0]. Women were shorter and had a higher median BMI than men, whereas serum creatinine concentrations were higher in men than in women (median 10.74 vs 8.81 mg/L; $p = 0.001$) (Table 1).

Table 1
Demographic, anthropometric, and serum creatinine characteristics of the study population overall and by sex.

Variable	Overall (N = 288)	Men (n = 272)	Women (n = 16)	p-value
Age, years	29.0 [24.0–36.0]	29.0 [25.0–36.0]	24.5 [22.0–33.0]	0.322
Weight, kg	70.0 [64.0–78.0]	70.0 [64.0–78.0]	70.0 [64.8–76.2]	0.723
Height, m	1.70 [1.70–1.80]	1.70 [1.70–1.80]	1.60 [1.60–1.70]	< 0.001
BMI, kg/m ²	23.6 [21.6–26.3]	23.4 [21.4–26.1]	27.3 [25.0–28.6]	< 0.001
Serum creatinine, mg/L	10.70 [9.56–11.63]	10.74 [9.65–11.66]	8.81 [7.36–10.27]	0.001
Data are median [Q1–Q3]. p-values compare men and women using the Mann–Whitney U test. No data were missing. BMI, body mass index; Q1/Q3, first/third quartile.				

Serum creatinine distribution and candidate reference interval

In the overall study population, serum creatinine had a mean concentration of 10.60 ± 1.93 mg/L and a median of 10.70 mg/L [9.56–11.63], with observed values ranging from 3.83 to 17.65 mg/L. The distribution was approximately symmetric, with a skewness of – 0.15 and excess kurtosis of 1.79.

Fifteen observations exceeded the Tukey 1.5 × interquartile-range fences. None exceeded the 3 × interquartile-range fences, and the Dixon–Reed procedure did not identify an observation meeting the prespecified exclusion criterion. All flagged observations were therefore retained in the primary analysis.

Among men (n = 272), the non-parametric central 95% serum creatinine reference interval was 6.50–15.10 mg/L, corresponding to 0.65–1.51 mg/dL or 57–134 µmol/L. The 90% confidence interval was 5.55–7.25 mg/L for the lower reference limit and 14.20–15.55 mg/L for the upper reference limit (Table 2 and Fig. 1).

Table 2

Serum creatinine distribution and candidate reference intervals in the overall population and by sex.

Group	n	Mean ± SD	Median [Q1–Q3]	Min–Max	LRL (P2.5)	90% CI for LRL	URL (P97.5)	90% CI for URL
Overall	288	10.60 ± 1.93	10.70 [9.56–11.63]	3.83–17.65	6.62	5.87–7.21	15.02	14.06–15.42
Men	272	10.69 ± 1.89	10.74 [9.65–11.66]	3.83–17.65	6.50	5.55–7.25	15.10	14.20–15.55
Women†	16	9.07 ± 1.98	8.81 [7.36–10.27]	6.62–13.00	6.63	6.62–7.13	12.76	10.68–13.00

Reference limits were estimated non-parametrically according to the CLSI EP28-A3c statistical framework. Ninety-percent confidence intervals were obtained by bootstrap resampling with 10,000 replicates. The male interval of 6.50–15.10 mg/L corresponds to 0.65–1.51 mg/dL or 57–134 µmol/L. †The female subgroup was below the recommended minimum of 120 reference individuals; female limits are therefore descriptive only. LRL, lower reference limit; URL, upper reference limit; SD, standard deviation.

In the overall population, the corresponding reference interval was 6.62–15.02 mg/L. Results for women are presented descriptively in Table 2 but were not considered sufficiently precise for sex-specific reference-interval estimation.

In a sensitivity analysis excluding the 15 observations flagged by the Tukey method, the male reference interval narrowed to 7.71–13.46 mg/L.

Associations of age, sex, and BMI with serum creatinine

Serum creatinine did not differ significantly across age groups (Kruskal–Wallis $p = 0.229$) or BMI categories ($p = 0.438$). Spearman correlations were also not significant for age ($r_s = 0.04$; $p = 0.502$) or BMI ($r_s = 0.02$; $p = 0.745$) (Supplementary Table S1).

In the full sample, multivariable linear regression showed that male sex was independently associated with higher serum creatinine concentration (adjusted $\beta = +1.74$ mg/L, 95% CI 0.67–2.82; $p = 0.001$). Neither age nor BMI was independently associated with mean serum creatinine concentration (Table 3).

Table 3
Associations of age, sex, and BMI with serum creatinine concentration.

Population / Variable	Increment	Crude β (95% CI)	p-value	Adjusted β (95% CI)	p-value
Overall population (n = 288)					
Age	per 10 years	−0.100 (−0.338 to 0.138)	0.411	−0.149 (−0.405 to 0.106)	0.252
Sex, men vs women	—	+ 1.626 (0.598 to 2.655)	0.002	+ 1.740 (0.666 to 2.815)	0.001
BMI	per 5 kg/m ²	−0.055 (−0.454 to 0.344)	0.788	+ 0.160 (−0.273 to 0.594)	0.468
Men only (n = 272)					
Age	per 10 years	—	—	−0.185 (−0.460 to 0.089)	0.185
BMI	per 5 kg/m ²	—	—	+ 0.214 (−0.239 to 0.668)	0.354
<i>Linear regression was performed on untransformed serum creatinine using HC3 heteroscedasticity-consistent standard errors. The adjusted overall model included age, sex, and BMI simultaneously ($R^2=0.042$). The male-only model included age and BMI simultaneously ($R^2=0.008$). β coefficients are expressed in mg/L per stated increment.</i>					

In the secondary analysis restricted to men ($n = 272$), age was not associated with mean serum creatinine ($\beta = -0.19$ mg/L per 10-year increase, 95% CI −0.46 to 0.09; $p = 0.185$), and BMI was also not significantly associated with mean creatinine ($\beta = +0.21$ mg/L per 5 kg/m² increase, 95% CI −0.24 to 0.67; $p = 0.354$). The model explained little of the variability in serum creatinine ($R^2=0.008$).

Discordance with the manufacturer-supplied reference interval

Among the 272 men, 61 (22.4%) had serum creatinine concentrations outside the manufacturer-supplied male reference interval of 7.0–12.0 mg/L. Nine men (3.3%) had concentrations below 7.0 mg/L, whereas 52 (19.1%) had concentrations above 12.0 mg/L.

In the adjusted modified Poisson regression model, each 5 kg/m² increase in BMI was associated with a higher prevalence of serum creatinine outside the manufacturer-supplied interval (adjusted prevalence ratio 1.58, 95% CI 1.09–2.31; p = 0.017). Age was not significantly associated with discordance (adjusted prevalence ratio 0.93 per 10-year increase, 95% CI 0.72–1.19; p = 0.539) (Table 4).

Table 4
Factors associated with serum creatinine outside the manufacturer-supplied reference interval among men.

Analysis	Variable	Increment	aPR	95% CI	p-value
Primary analysis, n = 272	Age	per 10 years	0.93	0.72–1.19	0.539
Primary analysis, n = 272	BMI	per 5 kg/m ²	1.58	1.09–2.31	0.017
Sensitivity analysis, n = 257*	Age	per 10 years	0.99	0.75–1.32	0.955
Sensitivity analysis, n = 257*	BMI	per 5 kg/m ²	1.56	1.01–2.43	0.047
<i>Modified Poisson regression with a log link and robust sandwich variance was used. The outcome was serum creatinine outside the manufacturer-supplied male reference interval (< 7.0 or > 12.0 mg/L). In the primary analysis, 61/272 men (22.4%) met this definition. *The sensitivity analysis excluded the 15 observations flagged by the Tukey 1.5×IQR rule. Age and BMI were included simultaneously in each model. aPR, adjusted prevalence ratio; BMI, body mass index.</i>					

After exclusion of the 15 Tukey-flagged observations, the association between BMI and discordance remained similar (adjusted prevalence ratio 1.56 per 5 kg/m² increase, 95% CI 1.01–2.43; p = 0.047).

Exploratory distributional analyses

Exploratory quantile regression suggested that associations of age and BMI with serum creatinine may differ across the creatinine distribution. Estimates were less stable at the upper quantiles and were considered hypothesis-generating; detailed results are provided in Supplementary Table S2. Published African serum creatinine reference intervals and analytical methods are summarized in Supplementary Table S3.

Discussion

In this study, we derived a candidate serum creatinine reference interval of 6.50–15.10 mg/L (0.65–1.51 mg/dL; 57–134 µmol/L) in apparently healthy Mauritanian adult male blood donors using an IDMS-traceable compensated Jaffé assay. The main finding was the substantial discordance between this locally derived interval and the manufacturer-supplied male reference interval of 7.0–12.0 mg/L. Overall, 22.4% of men had creatinine concentrations outside the manufacturer interval, with most discordant values occurring above its upper limit. These findings suggest that direct adoption of manufacturer-

supplied reference limits may not adequately reflect the distribution of serum creatinine in this population and support local verification before routine use.

The distinction between reference intervals and clinical decision thresholds is particularly important for serum creatinine. Reference intervals describe the distribution of values in a defined reference population, whereas the diagnosis and staging of kidney disease rely on a broader clinical framework that includes estimated glomerular filtration rate, albuminuria, persistence over time, and other markers of kidney damage. Therefore, the wider interval observed in the present study should not be interpreted as evidence that higher creatinine concentrations are necessarily clinically normal or that established criteria for chronic kidney disease should be modified. Rather, our findings concern the appropriateness of laboratory reference limits for this specific population and analytical method.

Published studies from African populations have reported heterogeneous serum creatinine reference values across countries and analytical settings [22–29]. The lower reference limit observed in the present study, 0.65 mg/dL, was identical to that reported by Bukabau et al. in healthy adult men from Central Africa, whereas our upper limit of 1.51 mg/dL was higher than the 1.22 mg/dL reported in that study [23]. It was also higher than the upper value of 1.36 mg/dL reported in Cameroon [22]. Other studies from West, East, and Southern Africa have likewise shown substantial between-population variability in creatinine distributions and renal-function markers [24–29]. Differences in age structure, sex distribution, body composition, dietary patterns, reference-population selection, pre-analytical conditions, and analytical methods may all contribute to this heterogeneity. Consequently, direct transfer of reference limits between African populations should be approached cautiously.

Men had higher serum creatinine concentrations than women in the present study, consistent with the established influence of sex and muscle mass on creatinine generation [4, 5, 18–20]. However, only 16 women were included, precluding reliable non-parametric estimation of a female-specific reference interval. The absence of a significant association between age and mean serum creatinine should also be interpreted in light of the relatively young age distribution of blood donors and the limited representation of older adults. Similarly, BMI was not independently associated with mean creatinine concentration. Because BMI does not distinguish lean mass from adipose mass, it may not adequately capture the body-composition component most directly related to creatinine production [4, 5].

An exploratory finding was the association between increasing BMI and a higher prevalence of serum creatinine values outside the manufacturer-supplied interval, despite the absence of an association between BMI and mean creatinine concentration. This result remained similar after exclusion of Tukey-flagged observations. The finding may indicate that the manufacturer interval does not perform uniformly across the range of body size represented in the study population. However, this interpretation should remain cautious because BMI is an imperfect surrogate for muscle mass and because potentially relevant determinants such as direct measures of lean mass, recent meat intake, creatine supplementation, hydration status, and recent strenuous exercise were unavailable. The modified

Poisson analysis should therefore be regarded as exploratory rather than as evidence that higher BMI itself causes discordant creatinine classification.

Exploratory quantile regression suggested that the associations of age and BMI with serum creatinine may vary across the creatinine distribution. BMI coefficients were larger at the upper percentiles than at the median, while negative age coefficients were observed at the 90th and 95th percentiles. These findings are hypothesis-generating and should not be used to define age- or BMI-specific reference limits. Estimates at the upper tails are inherently less stable because they depend on relatively few observations, and confirmation would require substantially larger samples with broader representation across age and body-composition strata.

Analytical methodology is central to the interpretation of creatinine reference intervals. Jaffé-based assays remain susceptible to interference from non-creatinine chromogens and may show method-specific bias compared with enzymatic assays [13, 14]. Compensation and IDMS traceability improve standardization but do not eliminate all residual analytical differences [15–17]. For this reason, the interval derived in the present study should be considered specific to the BioSystems A15 compensated Jaffé method and the analytical conditions under which it was obtained. It should not be transferred directly to laboratories using different platforms or measurement principles without local verification.

The sensitivity of the reference limits to outlier handling also deserves attention. Fifteen observations exceeded the Tukey $1.5 \times$ interquartile-range fences, and exclusion of these observations narrowed the male reference interval from 6.50–15.10 to 7.71–13.46 mg/L. Nevertheless, the flagged concentrations were biologically plausible, none exceeded the $3 \times$ interquartile-range fences, and the Dixon–Reed criterion did not support their exclusion. Because statistical outlier rules alone do not establish that a result is erroneous, these values were retained in the primary analysis and the narrower interval was reported as a sensitivity analysis. The magnitude of this difference illustrates the uncertainty inherent in estimating reference-distribution tails and reinforces the need for independent validation.

This study has several strengths. Reference limits were derived using a non-parametric CLSI EP28-A3c framework [6] with bootstrap confidence intervals for both reference limits. The analytical method, calibration traceability, and quality-control procedures were documented. Potential outliers were evaluated using prespecified statistical criteria together with biological plausibility rather than being removed solely to produce a narrower interval. In addition, the study quantified discordance with an externally supplied manufacturer interval rather than relying only on visual comparison of reference limits. Finally, the study provides creatinine reference data from Mauritania, a population for which locally derived information remains limited.

Several limitations should also be considered. Participants were blood donors recruited at a single urban centre and were predominantly young men; therefore, the findings cannot be generalized directly to women, older adults, rural populations, or persons who do not meet blood-donation eligibility criteria. Obesity and known chronic diseases were excluded as part of reference-population selection, further restricting generalizability. No study-specific renal assessment using cystatin C, urinalysis, albuminuria

testing, or kidney imaging was performed, so subclinical kidney disease cannot be completely excluded. Information on muscle mass, hydration status, recent meat intake, creatine supplementation, and strenuous physical activity was unavailable. In addition, although manufacturer-reported analytical performance and IDMS traceability were documented, complete study-period estimates of analytical imprecision and measurement uncertainty were not available.

Overall, these findings support the proposed 6.50–15.10 mg/L interval as a candidate, method-specific serum creatinine reference interval for apparently healthy Mauritanian adult male blood donors rather than as an immediately implementable replacement for existing laboratory limits. The 22.4% discordance with the manufacturer-supplied interval highlights the importance of local verification. Independent validation in larger, multicentre Mauritanian populations with adequate representation of women, older adults, and broader body-composition profiles is required before routine laboratory implementation.

Conclusions

A candidate serum creatinine reference interval of 6.50–15.10 mg/L (0.65–1.51 mg/dL; 57–134 μ mol/L) was derived in apparently healthy Mauritanian adult male blood donors using an IDMS-traceable compensated Jaffé assay. The interval was wider than the manufacturer-supplied male reference interval of 7.0–12.0 mg/L, with 22.4% of men classified outside the latter, predominantly above its upper limit.

These findings support local verification of manufacturer-supplied creatinine reference limits. The proposed interval should be considered method-specific and requires independent validation in larger, more diverse Mauritanian populations before routine implementation.

Abbreviations

aPR

adjusted prevalence ratio

BMI

body mass index

CI

confidence interval

CLSI

Clinical and Laboratory Standards Institute

eGFR

estimated glomerular filtration rate

HC3

heteroscedasticity-consistent type 3 standard errors

IDMS

isotope-dilution mass spectrometry

IQR

interquartile range

LRL

lower reference limit

PR

prevalence ratio

SD

standard deviation

URL

upper reference limit.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the University of Nouakchott, Mauritania (approval no. 11/23, 4 July 2023; renewed under no. 0004, 19 January 2025). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment.

Consent for publication

Not applicable.

Availability of data and materials

The dataset analysed during the current study is not publicly available because it contains participant-level research data subject to ethical and confidentiality restrictions. De-identified data may be made available from the corresponding author upon reasonable request and subject to approval consistent with the conditions of the study's ethical authorization.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KB contributed to conceptualization, methodology, investigation, data curation, formal analysis, validation, and manuscript review and editing. MB contributed to conceptualization, methodology, investigation, data curation, validation, and manuscript review and editing. WC contributed to conceptualization, methodology, validation, and manuscript review and editing. COM contributed to methodology, investigation, and data curation. MVOEK contributed to conceptualization, methodology, formal analysis, validation, project administration, supervision, drafting of the original manuscript, and manuscript review and editing. All authors read and approved the final manuscript.

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References

1. Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int.* 2024;105(4S):S117–314.
2. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604–12. 10.7326/0003-4819-150-9-200905050-00006.
3. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med.* 2021;385(19):1737–49. 10.1056/NEJMoa2102953.
4. Delanaye P, Cavalier E, Pottel H. Serum creatinine: not so simple! *Nephron.* 2017;136(4):302–8. 10.1159/000469669.
5. Peake M, Whiting M. Measurement of serum creatinine—current status and future goals. *Clin Biochem Rev.* 2006;27(4):173–84.
6. Clinical and Laboratory Standards Institute. Defining, establishing, and verifying reference intervals in the clinical laboratory. 3rd ed. CLSI guideline EP28-A3c. Wayne, PA: Clinical and Laboratory Standards Institute; 2010.
7. Ozarda Y. Reference intervals: current status, recent developments and future considerations. *Biochem Med (Zagreb).* 2016;26(1):5–16. 10.11613/BM.2016.001.
8. Jones G, Barker A. Reference intervals. *Clin Biochem Rev.* 2008;29(Suppl 1):S93–7.
9. Ceriotti F, Henny J. Are my laboratory results normal? Considerations to be made concerning reference intervals and decision limits. *EJIFCC.* 2008;19(2):106–14.
10. Ichihara K, Ozarda Y, Barth JH, Klee G, Qiu L, Erasmus R, et al. A global multicenter study on reference values: 1. Assessment of methods for derivation and comparison of reference intervals.

- Clin Chim Acta. 2017;467:70–82. 10.1016/j.cca.2016.09.016.
11. Ichihara K, Ozarda Y, Barth JH, Klee G, Qiu L, Erasmus R, et al. A global multicenter study on reference values: 2. Exploration of sources of variation across the countries. Clin Chim Acta. 2017;467:83–97. 10.1016/j.cca.2016.09.015.
 12. Ozarda Y, Ichihara K, Barth JH, Klee G, Committee on Reference Intervals and Decision Limits, International Federation for Clinical Chemistry and Laboratory Medicine. Protocol and standard operating procedures for common use in a worldwide multicenter study on reference values. Clin Chem Lab Med. 2013;51(5):1027–40. 10.1515/ccim-2013-0249.
 13. Delanghe JR, Speeckaert MM. Creatinine determination according to Jaffé—what does it stand for? NDT Plus. 2011;4(2):83–6. 10.1093/ndtplus/sfq211.
 14. Drion I, Cobbaert C, Groenier KH, Weykamp C, Bilo HJG, Wetzels JFM, et al. Clinical evaluation of analytical variations in serum creatinine measurements: why laboratories should abandon Jaffé techniques. BMC Nephrol. 2012;13:133. 10.1186/1471-2369-13-133.
 15. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem. 2006;52(1):5–18. 10.1373/clinchem.2005.0525144.
 16. Piéroni L, Delanaye P, Boutten A, Bargnoux AS, Rozet E, Delatour V, et al. A multicentric evaluation of IDMS-traceable creatinine enzymatic assays. Clin Chim Acta. 2011;412(23–24):2070–5. 10.1016/j.cca.2011.07.012.
 17. Jassam N, Weykamp C, Thomas A, Secchiero S, Sciacovelli L, Plebani M, et al. Post-standardization of routine creatinine assays: are they suitable for clinical applications? Ann Clin Biochem. 2017;54(3):386–94. 10.1177/0004563216664541.
 18. Pottel H, Vrydags N, Mahieu B, Vandewynckele E, Croes K, Martens F. Establishing age- and sex-related serum creatinine reference intervals from hospital laboratory data based on different statistical methods. Clin Chim Acta. 2008;396(1–2):49–55. 10.1016/j.cca.2008.06.017.
 19. Finney H, Newman DJ, Price CP. Adult reference ranges for serum cystatin C, creatinine and predicted creatinine clearance. Ann Clin Biochem. 2000;37(Pt 1):49–59. 10.1258/0004563001901524.
 20. Erlandsen EJ, Randers E. Reference intervals for plasma cystatin C and plasma creatinine in adults using methods traceable to international calibrators and reference methods. J Clin Lab Anal. 2018;32(6):e22433. 10.1002/jcla.22433.
 21. Verma M, Khadapkar R, Sahu PS, Das BR. Comparing age-wise reference intervals for serum creatinine concentration in a reality check of the recommended cut-off. Indian J Clin Biochem. 2006;21(2):90–4. 10.1007/BF02912921.
 22. Edinga-Melenge BE, Yakam AT, Nansseu JR, Bilong C, Belinga S, Minkala E, et al. Reference intervals for serum cystatin C and serum creatinine in an adult sub-Saharan African population. BMC Clin Pathol. 2019;19:4. 10.1186/s12907-019-0086-7.

23. Bukabau JB, Cavalier E, Pottel H, Nkodila AN, Makulo JRR, Mokoli VM, et al. Reference intervals for serum creatinine for healthy adults in central Africa: a post-hoc analysis. *BMC Nephrol.* 2025;26:607. 10.1186/s12882-025-04538-w.
24. Yayo E, Ayé M, Yao C, Gnionsahé A, Attoungbré ML, Cavalier E, et al. Measured and estimated glomerular filtration rate: reference values in West Africa. *Nephrol Dial Transpl.* 2018;33(7):1176–80. 10.1093/ndt/gfx244.
25. Abbam G, Tandoh S, Tetteh M, Afrifah DA, Annani-Akollor ME, Owiredo EW, et al. Reference intervals for selected haematological and biochemical parameters among apparently healthy adults in different eco-geographical zones in Ghana. *PLoS ONE.* 2021;16(1):e0245585. 10.1371/journal.pone.0245585.
26. Eller LA, Eller MA, Ouma B, Kataaha P, Kyabaggu D, Tumusiime R, et al. Reference intervals in healthy adult Ugandan blood donors and their impact on conducting international vaccine trials. *PLoS ONE.* 2008;3(12):e3919. 10.1371/journal.pone.0003919.
27. Karita E, Ketter N, Price MA, Kayitenkore K, Kaleebu P, Nanvubya A, et al. CLSI-derived hematology and biochemistry reference intervals for healthy adults in eastern and southern Africa. *PLoS ONE.* 2009;4(2):e4401. 10.1371/journal.pone.0004401.
28. Miri-Dashe T, Osawe S, Daniel MTN, Choji RP, Mamman I, Deme K, et al. Comprehensive reference ranges for hematology and clinical chemistry laboratory parameters derived from normal Nigerian adults. *PLoS ONE.* 2014;9(5):e93919. 10.1371/journal.pone.0093919.
29. Fiseha T, Alemayehu E, Mohammed Adem O, Eshetu B, Gebreweld A. Reference intervals for common clinical chemistry parameters in healthy adults of Northeast Ethiopia. *PLoS ONE.* 2022;17(11):e0276825. 10.1371/journal.pone.0276825.
30. BioSystems SA. Creatinine Jaffé-compensated. Instructions for Use, Ref. 12502. Barcelona, Spain: BioSystems S.A.
31. Ichihara K, Boyd JC. An appraisal of statistical procedures used in derivation of reference intervals. *Clin Chem Lab Med.* 2010;48(11):1537–51. 10.1515/CCLM.2010.319.

Figures

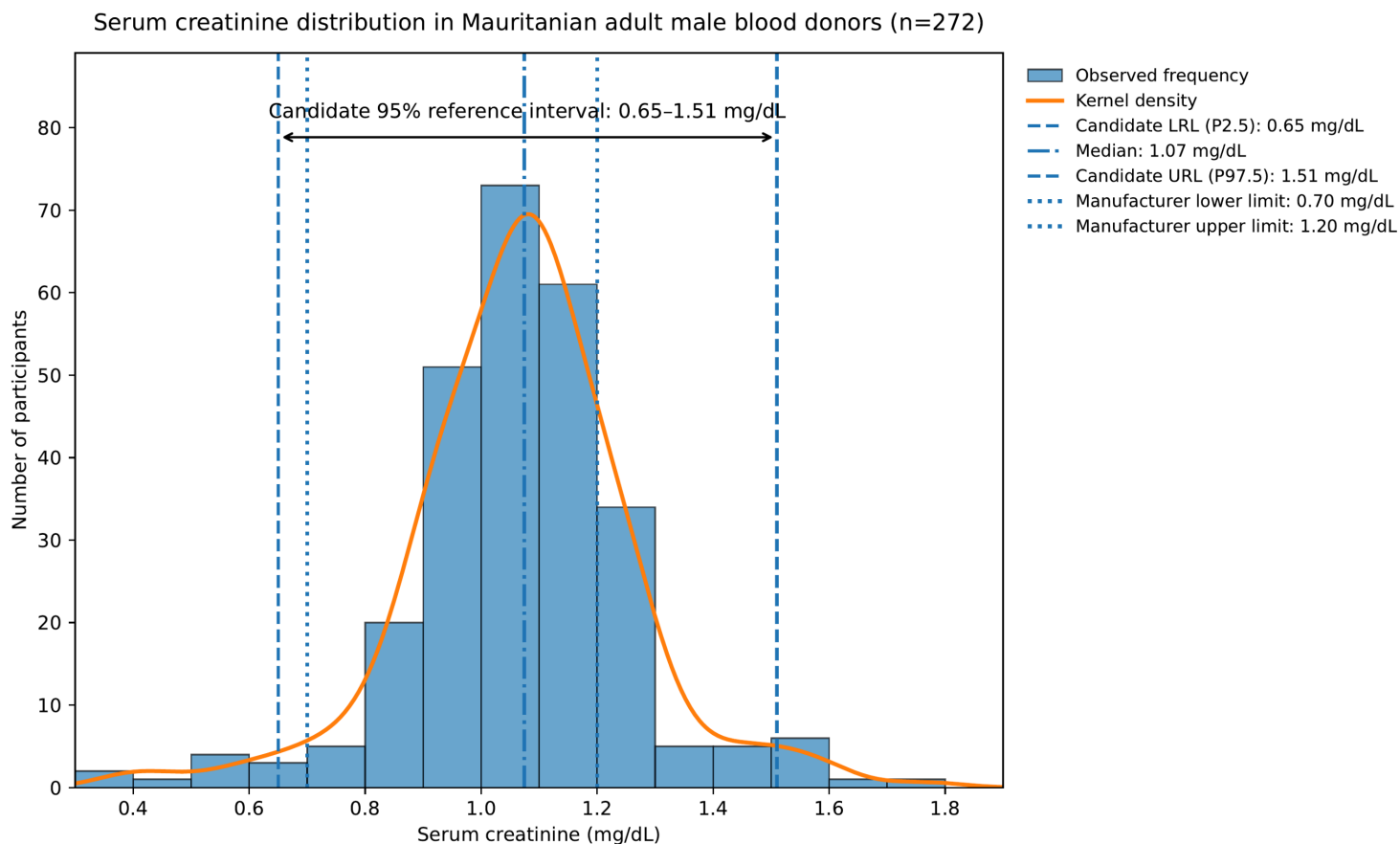


Figure 1

Distribution of serum creatinine and candidate reference limits among Mauritanian adult male blood donors (n=272). Histogram bars show the observed serum creatinine distribution, and the solid curve represents the kernel-density estimate. Vertical lines indicate the median (1.07 mg/dL), candidate lower reference limit (P2.5, 0.65 mg/dL), and candidate upper reference limit (P97.5, 1.51 mg/dL). The manufacturer-supplied male reference interval of 0.70–1.20 mg/dL is shown for comparison.

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