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Diagnostic accuracy of cardiac CT attenuation for anemia detection and severity grading

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Abstract

Background: Anemia is a prevalent hematological disorder associated with substantial morbidity among hospitalized patients. This study aimed to evaluate the diagnostic accuracy of non-contrast cardiac computed tomography (CT) attenuation measurements obtained from different cardiac regions for detecting anemia and grading its severity.

Methods: This cross-sectional study included 336 patients who underwent non-contrast thoracic CT imaging. Attenuation values were measured in the left ventricle, right ventricle, interventricular septum, and aortic arch and were compared with hemoglobin levels obtained from complete blood count tests. ROC curve analysis, independent-samples t-tests, Mann-Whitney U tests, one-way ANOVA, and correlation analyses were performed to evaluate diagnostic performance and subgroup differences. Significance was set at P-Value < 0.05.

Results: Aortic arch attenuation demonstrated the highest diagnostic accuracy for overall anemia detection (Area under the curve [AUC] = 0.668; Sensitivity = 71.3%; Specificity = 55.9%), followed by left ventricular attenuation (AUC = 0.635; Sensitivity = 44.0%; Specificity = 76.5%). Diagnostic performance improved for moderate to severe anemia (AUCs ranging from 0.690 to 0.757), whereas discrimination of mild anemia remained limited (AUCs ≤ 0.589). Attenuation values in the left ventricle, right ventricle, and aortic arch showed significant inverse correlations with hemoglobin levels (Spearman's rho = -0.275 to -0.297; P-Value < 0.001), while no significant association was observed in the septum. Gender-stratified analyses showed consistent reductions in attenuation among anemic patients of both genders.

Conclusion: Non-contrast cardiac CT attenuation measurements showed statistically significant associations with hemoglobin levels but demonstrated limited discriminatory performance for anemia detection, particularly in mild cases. Attenuation values obtained during routine thoracic imaging may provide complementary opportunistic information; however, further validation studies are required before clinical implementation.

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Highlights

What is current knowledge?

- Non-contrast thoracic CT attenuation values may correlate with hemoglobin concentration.
- Previous studies have suggested a potential role for CT attenuation in opportunistic anemia detection.
- Diagnostic performance and optimal attenuation thresholds reported in the literature remain inconsistent.
- Evidence regarding multi-regional cardiac attenuation assessment and anemia severity grading remains limited.

What is new here?

- This study simultaneously evaluated attenuation values in the left ventricle, right ventricle, interventricular septum, and aortic arch using routine non-contrast thoracic CT.
- Aortic arch attenuation demonstrated the highest diagnostic performance among the evaluated regions.
- CT attenuation measurements discriminated moderate-to-severe anemia more effectively than mild anemia.
- Gender-stratified analyses demonstrated consistent attenuation reduction patterns in both male and female patients.
- The findings support the potential use of routine thoracic CT as an opportunistic complementary tool for anemia assessment.

Introduction

Anemia is one of the most common hematologic disorders worldwide and is associated with substantial morbidity, mortality, and prolonged hospitalization, particularly among critically ill and hospitalized patients. According to the World Health Organization (WHO), anemia affects a considerable proportion of the global population and contributes to impaired oxygen delivery, reduced functional capacity, and adverse clinical outcomes (1). Early recognition of anemia is therefore clinically important, especially among patients undergoing routine diagnostic imaging in emergency and inpatient settings.

Computed tomography (CT) is widely used in thoracic and cardiovascular imaging and may offer an opportunity for opportunistic anemia assessment without additional invasive procedures or delays in laboratory testing. Several studies have suggested that anemia-related reductions in hemoglobin concentration may influence blood attenuation values on non-contrast CT imaging. Prior investigations have reported associations between decreased CT attenuation in vascular and cardiac structures and lower hemoglobin levels, particularly in the thoracic aorta and cardiac chambers (2-5). Nevertheless, the absence of standardized attenuation thresholds and the limited availability of data on gender-specific differences complicate clinical adoption. Moreover, the lack of a strong correlation between CT attenuation and hemoglobin levels in some studies raises concerns regarding the reliability of this approach (6). Overall, reported diagnostic performance has varied considerably across studies, and the clinical utility of attenuation-based anemia detection remains uncertain.

Abbasi et al. (7) demonstrated that non-contrast chest CT scans can serve as a useful tool for anemia detection through both objective density measurements and subjective visual signs. Their analysis showed that the aortic ring sign is highly sensitive for screening, whereas the interventricular septum sign provides high specificity for confirming the condition. In addition, the study identified an objective threshold of 20 HU within the aortic arch as the most effective parameter for predicting severe anemia.

Damodaran Kumar et al. (8) demonstrated that unenhanced thoracic CT scans offer high diagnostic accuracy for detecting anemia and evaluating its severity when objective blood attenuation values are assessed alongside subjective imaging markers.

Most previous studies have focused on single anatomical regions or contrast-enhanced imaging protocols, whereas evidence regarding multi-regional attenuation assessment using routine non-contrast thoracic CT remains limited. In addition, the ability of CT attenuation measurements to distinguish anemia severity levels and the consistency of these measurements across male and female patients remain incompletely understood.

Therefore, the present study aimed to evaluate the diagnostic performance of non-contrast cardiac CT attenuation measurements obtained from multiple cardiac regions, including the left ventricle, right ventricle, interventricular septum, and aortic arch, for detecting anemia and grading its severity in hospitalized patients. The study also assessed gender-stratified attenuation patterns and correlations between attenuation values and hemoglobin levels.

Methods

Study design and setting

This cross-sectional observational study was conducted at Shahid Sayyad Shirazi Hospital, Gorgan, Iran, during the first half of 2022. The study evaluated the diagnostic accuracy of non-contrast cardiac computed tomography (CT) attenuation measurements for detecting anemia and grading its severity. Quantitative attenuation values obtained from different cardiac regions were compared with contemporaneous hemoglobin levels obtained from complete blood count (CBC) tests.

Study population

A total of 336 adult patients who underwent routine non-contrast thoracic CT examinations at Shahid Sayyad Shirazi Hospital were included. Patients were selected using purposive sampling based on the availability of corresponding hemoglobin measurements obtained during the same clinical visit.

Inclusion criteria comprised the availability of both non-contrast thoracic CT images and CBC results. Patients with a history of intravenous or oral contrast administration within one week before CT imaging were excluded to avoid interference with attenuation measurements. Additional exclusion criteria included incomplete clinical data, severe motion artifacts affecting image quality, and unwillingness to participate in the study.

Both male and female patients were included, and demographic information was collected to evaluate potential gender-related differences in CT attenuation values.

CT acquisition and attenuation measurements

CT imaging was performed using a Siemens Somatom scanner with a standardized non-contrast thoracic imaging protocol. Images were acquired at a slice thickness of 1 mm during breath-hold to minimize motion artifacts.

Attenuation values were measured in Hounsfield Units (HU) by a trained member of the radiology team in the following regions of interest (ROIs): left ventricle (LV), right ventricle (RV), interventricular septum, and aortic arch. Representative ROI placements are shown in Figure 1 (Original work).

To ensure consistency, all attenuation measurements were obtained using the same imaging workstation and a standardized ROI placement technique. CT scanner calibration was performed according to the manufacturer's recommendations before image acquisition.

Hemoglobin assessment and anemia classification

Hemoglobin levels were obtained from routine complete blood count (CBC) tests performed during the same clinical encounter as CT imaging. Anemia severity was classified according to World Health Organization (WHO) criteria (9) as severe (Hb < 8.0 g/dL), moderate (Hb 8.0-10.9 g/dL), mild (Hb 11.0-11.9 g/dL for women and 11.0-12.9 g/dL for men), and normal hemoglobin levels (Hb ≥ 12.0 g/dL for women and ≥ 13.0 g/dL for men).

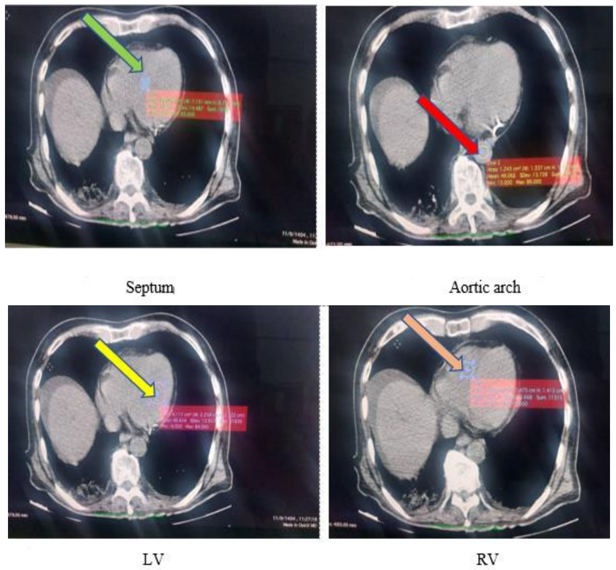

Figure 1. Representative non-contrast axial cardiac CT images demonstrating the regions of interest (ROIs) used for attenuation measurements in the left ventricle (LV), right ventricle (RV), interventricular septum, and aortic arch.

Statistical analysis

Statistical analyses were performed using SPSS 25.0 (IBM Inc., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were presented as frequencies and percentages.

The normality of data distribution was assessed using the Shapiro-Wilk test and visual inspection of histograms. Homogeneity of variances was evaluated using Levene's test. Parametric statistical tests were applied when assumptions of normality and variance homogeneity were satisfied; otherwise, nonparametric alternatives were used.

Comparisons between anemic and non-anemic groups were performed using independent-samples t-tests for normally distributed variables and Mann-Whitney U tests for non-normally distributed variables. One-way analysis of variance (ANOVA) was used to compare attenuation values across anemia severity groups.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of CT attenuation measurements for anemia detection and to determine optimal attenuation cut-off values. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) were calculated.

Correlations between hemoglobin levels and CT attenuation values were assessed using Spearman's rho and Kendall's tau-b correlation coefficients. Significance was set at P-Value < 0.05.

Results

This study evaluated the diagnostic accuracy of cardiac CT attenuation for detecting anemia and assessing its severity in patients admitted to Sayyad Shirazi Hospital in Gorgan, Iran, during the first six months of 1401 (Persian calendar, corresponding to 2022). A total of 336 patients, including 145 females (43.2%) and 191 males (56.8%), who underwent non-contrast chest CT scans were included and categorized into severe, moderate, mild, and normal hemoglobin groups according to the WHO criteria described in the Methods section.

Assessment of statistical assumptions showed that several attenuation variables approximated a normal distribution based on Shapiro-Wilk testing and histogram inspection, whereas selected subgroup distributions deviated from normality. Levene's test indicated acceptable homogeneity of variances for ANOVA-based comparisons. Accordingly, parametric analyses were applied when assumptions were satisfied, and nonparametric tests were used for non-normally distributed variables.

Left ventricular (LV) measurements ranged from 16 to 68 mm, with a mean of 38.21 (SD = 7.734); right ventricular (RV) measurements ranged from 18 to 72, with a mean of 37.81 (SD = 7.686); septal measurements ranged from 20 to 58, with a mean of 39.33 (SD = 6.870); and aortic arch measurements ranged from 13 to 65, with a mean of 38.70 (SD = 7.455). Hemoglobin (Hb) levels were distributed as follows: 39.6% of participants had moderate levels, 25.3% had mild levels, 20.2% had normal levels, and 14.9% had severe levels. Gender-specific analysis revealed that females had higher proportions of severe (19.3% vs. 11.5% in males) and normal (23.4% vs. 17.8%) Hb levels, whereas males had a higher proportion of mild levels (31.9% vs. 16.6%). The prevalence of moderate Hb levels was comparable between genders, with 40.7% in females and 38.7% in males.

The primary aim was to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of CT attenuation in the right ventricle (RV), left ventricle (LV), interventricular septum, and aortic arch for anemia detection and severity grading. Receiver operating characteristic (ROC) curve analysis was used to establish optimal cut-off points.

For anemia detection (Presence vs. Absence), CT attenuation values in the RV, LV, septum, and aortic arch were compared between patients with and without anemia. ROC analysis identified optimal cut-off values for CT attenuation in the left ventricle (LV), right ventricle (RV), septum, and arch, as presented in Table 1. ROC curve analysis comparing anemic and non-anemic patients showed that the aortic arch had the highest area under the curve (AUC = 0.668; 95% CI: 0.596-0.741; P-Value < 0.001), whereas the septum had the lowest AUC (0.536; 95% CI: 0.456-0.615; P-Value = 0.365), which was not statistically significant. At the selected cut-off points, sensitivity ranged from 41.0% (RV) to 83.2% (Septum), and specificity ranged from 27.9% (Septum) to 80.9% (RV). The positive predictive value (PPV) and negative predictive value (NPV) varied accordingly, with the arch showing a PPV of 44.3% and an NPV of 79.8% at a disease prevalence of 33%. Detailed diagnostic metrics for each cardiac region are summarized in Table 1.

The diagnostic performance of cardiac CT attenuation values in distinguishing different anemia severity levels from normal hemoglobin levels was evaluated using ROC analysis and associated metrics (Table 2). In mild anemia, the area under the curve (AUC) for all four cardiac regions (LV, RV, septum, and arch) was close to or below 0.6, with the highest value observed for the aortic arch (AUC=0.589, P-Value = 0.060), indicating weak discriminatory power. Sensitivity was high for the LV and septum (≥ 80%), but specificity was low (≤ 28%), resulting in low overall accuracy (~45%).

For moderate anemia, discriminatory performance improved, particularly for the aortic arch (AUC=0.690, P-Value < 0.001) and RV (AUC=0.668, P-Value < 0.001). Sensitivity and specificity became more balanced, especially in the arch, with a sensitivity of 75.19% and a specificity of 55.88%. Accuracy increased to approximately 62-69%.

In patients with severe anemia, diagnostic accuracy was highest, with the LV (AUC=0.757) and arch (AUC=0.745) showing strong discrimination (P-Value < 0.001). Sensitivity and specificity across the evaluated regions ranged from 50-68% and 72-85%, respectively, with corresponding accuracies above 70%. The positive predictive value (PPV) increased consistently with anemia severity, whereas negative predictive values (NPV) remained relatively stable (Around 70-82%) across all comparisons. Overall, CT attenuation was more effective for identifying moderate to severe anemia than mild anemia.

As summarized in Table 3, mean CT attenuation values for the left ventricle, right ventricle, septum, and aortic arch were compared between patients with and without anemia in the overall cohort and after stratification by gender. Based on the normality test results, parametric comparisons were used for LV and aortic arch attenuation, whereas nonparametric tests were used for RV and septal attenuation. Overall, anemic patients had significantly lower LV attenuation (Mean difference -3.68 HU, 95% CI -5.71 to -1.65; P-Value < 0.001) and aortic arch attenuation (-4.51 HU, 95% CI -6.44 to -2.57; P-Value < 0.001), with a modest but significant reduction in RV attenuation (-2.89 HU, 95% CI -4.93 to -0.86; P-Value = 0.005). Septal attenuation did not differ according to anemia status (P-Value = 0.461). Among men, LV (-3.66 HU; 95% CI -6.66 to -0.67; P-Value = 0.017) and aortic arch (-3.85 HU; 95% CI -6.41 to -1.30; P-Value = 0.003) attenuation remained significantly lower in anemic patients, whereas RV attenuation showed a trend in parametric testing (P-Value = 0.091) but reached significance using the Mann-Whitney U test (P-Value = 0.036); septal values were unaffected (P-Value = 0.244). In women, LV (-4.13 HU; 95% CI -6.76 to -1.51; P-Value = 0.002), RV (-3.84 HU; 95% CI -6.47 to -1.21; P-Value = 0.005), and aortic arch (-5.63 HU; 95% CI -8.55 to -2.70; P-Value < 0.001) attenuation values were all significantly reduced in anemia, whereas septal attenuation again showed no difference (P-Value = 0.661) (Table 2).

Table 1. Receiver operating characteristic (ROC) analysis and diagnostic performance of CT attenuation measurements for anemia detection

Region	Cut-Off	AUC	P-Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
LV	36.5	0.635	0.001	44.0	76.5	48.0	73.5
RV	35.5	0.626	0.001	41.0	80.9	51.4	73.6
Septum	45.5	0.536	0.365	83.2	27.9	36.3	77.2
Arch	41.5	0.668	< 0.001	71.3	55.9	44.3	79.8

Note: P-values represent the statistical significance of ROC curve analyses for discrimination between anemic and non-anemic patients (Testing whether AUC differs significantly from 0.5). PPV and NPV were calculated based on a disease prevalence of 33%.

Table 2. Diagnostic performance of cardiac CT attenuation in detecting anemia severity

Comparison	Region	AUC	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Mild vs Normal	LV	0.543	82.35	26.47	44.91	35.55	75.28
	RV	0.518	28.24	80.88	63.51	42.11	69.59
	Septum	0.500	80.00	27.94	45.12	35.35	73.93
	Arch	0.589	34.12	80.88	65.45	46.78	71.37
Moderate vs Normal	LV	0.647	63.16	60.29	61.24	43.93	76.87
	RV	0.668	45.11	80.88	69.08	53.75	74.95
	Septum	0.547	84.96	27.94	46.76	36.74	79.05
	Arch	0.690	75.19	55.88	62.25	45.63	82.06
Severe vs Normal	LV	0.757	66.00	76.47	73.02	58.01	82.04
	RV	0.698	50.00	85.29	73.65	62.61	77.60
	Septum	0.566	38.00	77.94	64.76	45.90	71.85
	Arch	0.745	68.00	72.06	70.72	54.52	82.05

Table 3. CT attenuation differences (Anemia vs. Non-anemia)

Population	Region	Test	Mean difference (HU)	P-Value
Overall (n=336)	LV	T-test (Equal var.)	- 3.68	< 0.001
	RV	T-test (Equal var.)	- 2.89	0.005
	Septum	Mann-Whitney U	- 0.69	0.365
	Aortic arch	T-test (Equal var.)	- 4.51	< 0.001
Men (n=191)	LV	T-test (Equal var.)	- 3.66	0.017
	RV	Mann-Whitney U	- 2.54	0.036
	Septum	Mann-Whitney U	- 1.47	0.175
	Aortic arch	T-test (Equal var.)	- 3.85	0.003
Women (n=145)	LV	T-test (Equal var.)	- 4.13	0.002
	RV	T-test (Equal var.)	- 3.84	0.005
	Septum	Mann-Whitney U	- 0.57	0.745
	Aortic arch	T-test (Equal var.)	- 5.63	< 0.001

Further analyses showed that CT attenuation differed significantly across anemia severity groups (Mild, moderate, and severe) for the left ventricle, right ventricle, and aortic arch, but not for the interventricular septum. Tests of normality and Levene's test confirmed that assumptions of homogeneity of variance were met for all regions. One-way ANOVA demonstrated a significant main effect of hemoglobin category on LV attenuation (P-Value < 0.001), RV attenuation (P-Value < 0.001), and aortic arch attenuation (P-Value = 0.002). By contrast, septal attenuation did not vary by anemia severity (P-Value = 0.304). These findings indicate that more severe anemia is associated with lower attenuation in the ventricular myocardium and aortic arch, whereas septal attenuation remains unaffected.

Correlation analyses revealed significant moderate inverse associations between hemoglobin level and CT attenuation in the ventricular myocardium and aortic arch, whereas septal attenuation showed no statistically meaningful relationship. Specifically, Kendall's tau-b indicated that hemoglobin was negatively correlated with LV attenuation (tau = -0.228, P-Value < 0.001), RV attenuation (tau = -0.212, P-Value < 0.001), and aortic arch attenuation (tau = -0.227, P-Value < 0.001), but not with septal attenuation (tau = -0.069, P-Value = 0.098). Consistent results were obtained using Spearman's rho, with hemoglobin correlating inversely with LV (rho = -0.297, P < 0.001), RV (rho = -0.275, P-Value < 0.001), and aortic arch (rho = -0.295, P-Value < 0.001) attenuation, while the septal correlation remained non-significant (rho = -0.090, P-Value = 0.100). These findings suggest that lower hemoglobin levels are associated with decreased CT attenuation in myocardial and vascular structures, but not in the interventricular septum (Table 4).

Table 4. Correlation coefficients between hemoglobin level and CT attenuation in cardiac regions

Region	Kendall's $\tau_{(b)}$	P-Value	Spearman's ρ	P-Value
LV	- 0.228	< 0.001	- 0.297	< 0.001
RV	- 0.212	< 0.001	- 0.275	< 0.001
Septum	- 0.069	0.098	- 0.090	0.100
Aortic Arch	- 0.227	< 0.001	- 0.295	< 0.001

Discussion

The findings of the present study suggest that non-contrast cardiac CT attenuation may have value as an adjunctive imaging indicator for anemia detection, particularly in moderate to severe cases. Among the evaluated regions, the aortic arch showed the highest discriminatory performance (AUC = 0.668), followed by the left ventricle (AUC = 0.635), although the overall discriminatory ability remained moderate. In contrast, attenuation measurements showed limited diagnostic utility for mild anemia, with AUC values generally below 0.60. These findings indicate that CT attenuation should not be considered a substitute for laboratory-based hemoglobin assessment. Rather, attenuation measurements obtained during routine thoracic imaging may provide supplementary information that helps identify patients who may benefit from further hematologic evaluation.

The present findings are generally consistent with previous studies reporting associations between CT attenuation and anemia-related changes in blood composition and tissue density. Foster et al. (2) demonstrated that unenhanced thoracic CT could predict anemia through changes in attenuation values, while Zhou et al. (3) suggested that thoracic aortic attenuation may provide moderate diagnostic discrimination for anemia severity. Similarly, Desaint et al. (4) described the "aortic ring sign" as a potentially useful imaging feature in anemic patients. The current study extends these observations by evaluating multiple cardiac regions simultaneously, including the left ventricle, right ventricle, interventricular septum, and aortic arch. Among these regions, the aortic arch and ventricular measurements showed the most consistent associations with hemoglobin levels, whereas septal attenuation demonstrated limited diagnostic relevance.

An important observation in this study was the progressive improvement in diagnostic performance with increasing anemia severity. Moderate and severe anemia showed substantially higher AUC values and more balanced sensitivity and specificity profiles compared with mild anemia. This pattern suggests that attenuation changes become more detectable as hemoglobin concentration decreases. However, the relatively modest performance metrics observed overall indicate that CT attenuation alone is unlikely to provide sufficient diagnostic accuracy for standalone anemia screening, particularly in mild cases. Taken together, these findings suggest that CT attenuation measurements may be useful as complementary imaging indicators rather than definitive diagnostic markers of anemia. The limited discriminatory performance observed in this study, particularly for mild anemia, indicates that attenuation-based assessment should be interpreted cautiously and in conjunction with standard laboratory evaluation.

Gender-stratified analyses demonstrated similar attenuation trends in men and women, with reductions in ventricular and aortic arch attenuation observed among anemic patients of both sexes. Although some attenuation differences appeared more pronounced in women, the overall diagnostic patterns remained broadly comparable between genders. These findings suggest that the relationship between CT attenuation and anemia is relatively consistent across sexes; however, larger multicenter studies are required to establish sex-specific thresholds with greater precision.

Several methodological limitations should be considered when interpreting the findings of this study. First, the study was conducted at a single center using purposive sampling, which may limit generalizability to broader populations and different imaging settings. Second, the cross-sectional design does not allow assessment of temporal changes in hemoglobin concentration or attenuation values over time. Third, although imaging acquisition parameters and ROI placement methods were standardized, attenuation measurements may still be influenced by technical factors, including scanner calibration, motion artifacts, slice selection, and interobserver variability. In addition, exclusion of patients with recent contrast administration may have introduced selection bias. Finally, although statistically significant associations were observed, the moderate AUC values indicate that CT attenuation measurements have limited standalone diagnostic capability.

Future research should focus on multicenter prospective validation studies with larger and more diverse populations to determine the reproducibility and clinical applicability of attenuation-based anemia assessment. Additional investigations using automated ROI analysis, spectral CT techniques, or machine-learning approaches may further improve diagnostic performance, particularly for mild anemia detection. Combining CT attenuation data with routinely available clinical and laboratory parameters may also enhance predictive accuracy and facilitate integration into opportunistic screening workflows.

Conclusion

The present study suggests that non-contrast cardiac CT attenuation measurements are associated with hemoglobin levels and may provide limited discriminatory value for identifying anemia, particularly in moderate to severe cases. Among the evaluated regions, the aortic arch demonstrated the highest overall performance, whereas attenuation measurements showed limited ability to distinguish mild anemia.

Although statistically significant associations were observed between attenuation values and hemoglobin concentration, the relatively low AUC values indicate that CT attenuation measurements should not be considered definitive or standalone diagnostic tools for anemia detection. Instead, attenuation measurements obtained from routinely acquired non-contrast thoracic CT scans may provide complementary opportunistic information that prompts further hematologic evaluation in selected patients.

Given the exploratory nature of these findings, additional multicenter prospective studies with external validation are required before attenuation-based thresholds can be considered for broader clinical application.

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Not applicable.

Ethical statement

The study protocol was approved by the institutional ethics committee of Golestan University of Medical Sciences (IR.GOUMS.REC.1401.444). Written informed consent was obtained from all participants before inclusion in the study. All patient data were anonymized before analysis, and no additional imaging or laboratory costs were imposed on participants for study purposes.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

S.L. interpreted the results and designed the study; M.M. prepared the data analysis; A.R. prepared the initial manuscript; and M.O. was responsible for clinical CTs.

Data availability statement

Data will be made available upon reasonable request.

Use of artificial intelligence

The authors declare that artificial intelligence tools were used for language editing and improving the clarity of the manuscript. The study design, data analysis, interpretation of results, and final conclusions were performed entirely by the authors, who take full responsibility for the content of this article.

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