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Prediction of anemia on enhanced computed tomography of the thorax using virtual non-contrast reconstructions

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Abstract

To determine if anemia can be predicted on enhanced computed tomography (CT) examinations of the thorax using virtual non-contrast (VNC) images, in order to support clinicians especially in diagnosing primary asymptomatic patients in daily routine.

In this monocentric study, 100 consecutive patients (50 with proven anemia), who underwent a contrast-enhanced CT examination of the thorax due to various indications were included. Attenuation was measured in the descending thoracic aorta, the intraventricular septum, and the left ventricle cavity both in the conventional contrast-enhanced and in the VNC images.

Two experienced radiologists annotated the delineation of a dense interventricular septum or a hyperattenuating aortic wall sign for all patients.

Hemoglobin levels were then correlated with the measured attenuation values, as well as the visualization of the aortic wall or interventricular septum.

Good correlation was shown between hemoglobin levels and CT attenuation values of the left ventricular cavity ($r=.59$), aorta ($r=.56$), and ratio between left ventricular cavity and the intraventricular septum ($r=.57$). Receiver operating characteristic curve revealed $\leq$ 36.5 hounsfield units (left ventricular cavity) as the threshold for diagnosing anemia. Predicting anemia by visualization of a hyperattenuating aortic wall or a dense interventricular septum yielded a specificity of 98% and 92%, respectively.

Predicting anemia on enhanced CT examinations using VNC is feasible. A threshold value of $\leq$ 36.5 hounsfield units (left ventricular cavity) best defines anemia. Aortic wall or interventricular septum visualization on VNC is a specific anemia indicator.

Abbreviations: AUC = area under the curve, CT = computed tomography, DECT = dual energy computed tomography, HU = Hounsfield Units, LV = left ventricle, ROC = receiver operating characteristic, ROI = region of interest, SDCT = dual layer spectral detector computed tomography, VNC = virtual non-contrast.

Keywords: dual-layer computed tomography, spectral detector computed tomography, virtual non-contrast, virtual non-contrast, anemia

1. Introduction

Anemia is a serious, often encountered medical condition in daily clinical routine, which can have serious effect on patients' outcome if not diagnosed. Although anemia can primarily be diagnosed by determining serum hemoglobin levels, asymptomatic patients and patients, where the clinician does not expect an anemic state, don't always undergo a complete blood count, this especially applying to oncological outpatients.

Ongoing improvements in temporal and spatial resolution of computed tomography (CT) have led to an increase in findings unrelated to the primary objectives of the examination.[1] In CT examinations of the thorax, such incidental findings are very common and can have a relevant influence on the treatment and outcome of patients.[2,3] A series of previously reported incidental findings on unenhanced CT examinations of the chest may be caused by an anemic condition:[4–10] a hyperattenuating myocardium or interventricular septum compared to a relatively hypodense left ventricular (LV) cavity ("interventricular septum sign") or a hyperattenuating aortic wall compared to a relatively hypodense aortic blood pool ("aortic ring sign").[4,7–10] However, interobserver variability is a relevant limitation of such a subjective approach[11] and therefore, objective measure-

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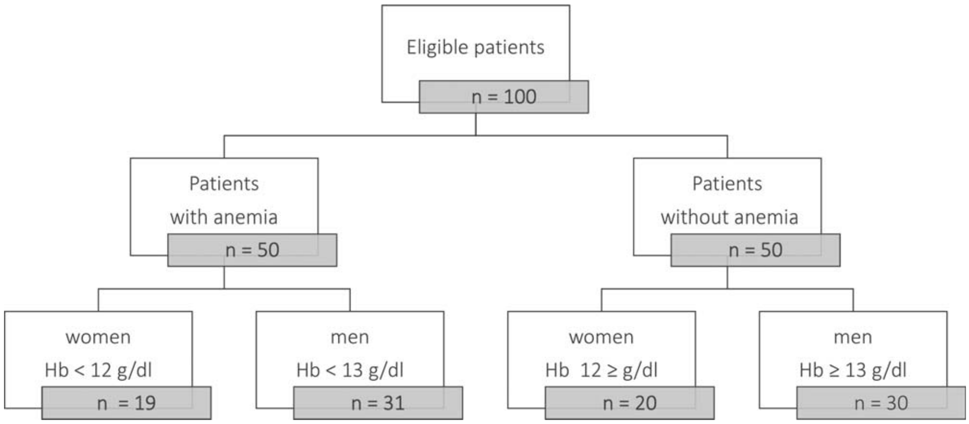

Figure 1. Diagram showing an overview of the included patients (n=100) considering both gender and anemic hemoglobin level distribution. Hb-Hemoglobin.

ment parameters are desirable to distinguish anemic from non-anemic individuals. For example one can analyze the density of the aortic lumen and/or the ventricles.[4,5,11] As the density of the vascular system is influenced by the contrast medium, these findings cannot be determined from contrast-enhanced CT examinations.

Until recently, in oncology positron emission tomography was one of the few CT-based image modalities especially helpful in visualizing metabolic processes especially in malignant processes.[12] With the introduction of dual energy computed tomography (DECT), lesions can now be further analyzed by differentiating material compositions using attenuation values, thus also calculating the iodine uptake. Further, special reconstruction algorithms can be used to calculate the so-called virtual non-contrast (VNC) images from contrast-enhanced examinations, providing surrogates for true unenhanced images. DECT enables the calculation of material-specific iodine maps, which can subsequently be subtracted from the original image to obtain VNC images. Moreover, with the dual layer spectral detector computed tomography (SDCT), one DECT variant, these VNC reconstructions are available also retrospectively, for every examination.

Since previous studies[4,7–10] found that anemia can be indicated in unenhanced CT scans, but in clinical routine a great number of CT scans of the thorax are contrast-enhanced examinations, the aim of this study was to determine if anemia can also be diagnosed on VNC images derived from venous phase scans of the thorax, as well to identify the best subjective and objective diagnostic parameters in order to support the clinician in his daily routine, especially in diagnosing primary asymptomatic patients.

2. Materials and methods

2.1. Study population

Ethical approval was waived due to the retrospective design of the study based on preexisting images (Ethics Committee of the Faculty of Medicine, University of Cologne, reference number 20–1209).

In this monocentric study, 100 consecutive patients from January 2017 to February 2018, who underwent a contrast-enhanced CT examination of the thorax due to various indications and had the hemoglobin level measured within a maximum of 7 days from the time of the CT scan, were included. None of the included patients received a blood transfusion in the period between blood examination and CT scan. Patients with acute symptoms/pathologies have not been included in this study, since this was beyond the primary purpose of the study. Anemia was defined as a hemoglobin level below 12 g/dl for women and below 13 g/dl for men.[13] The study population consisted of 50 patients with proven anemia and 50 nonanemic patients (Fig. 1).

2.2. Image acquisition and post-processing

All examinations were performed on a clinical 128-slice SDCT - (IQon, Philips Healthcare; *Best, The Netherlands*). Patients were scanned supine in cranio-caudal direction during inspirational breath-hold. The clinical routine protocol includes a venous phase imaging of the chest obtained after a bolus application of 100 ml non-ionic, iodinated contrast media (Accupaque 350 mg/ml; GE Healthcare, Little Chalfort, UK) injected via an antecubital vein at a flow rate of 3 ml/s followed by a 30 ml saline chaser. Bolus-tracking technique was activated in all cases, starting the examination with a 60 seconds scan delay once a trigger threshold of 150 Hounsfield units (HU) has been reached within the region of interest (ROI) placed in the descending aorta.

The following scanning parameters were kept constant in all scans: collimation - 2 × 64 × 0.625 mm; gantry rotation time - 0.33 seconds; pitch – 0.671; tube current - 120 kVp, matrix - 512 × 512; dose modulation type: DoseRight 3D-DOM (Philips Healthcare; Best, the Netherlands). All images were reconstructed in axial plane with a slice thickness of 2 mm and a section increment of 1 mm.

Conventional venous phase images (120 kV polyenergetic) were reconstructed using a hybrid-iterative reconstruction algorithm as in clinical routine (iDose 4, strength level 3, Rekon B; Philips Healthcare, Best, The Netherlands). For reconstruction of VNC images, a spectral reconstruction algorithm was used (Spectral, B, level 3, Philips Healthcare, Best, the Netherlands).

2.3. Qualitative image analysis

Two radiologists with three and four years of experience in cardiothoracic and CT imaging independently assessed the VNC

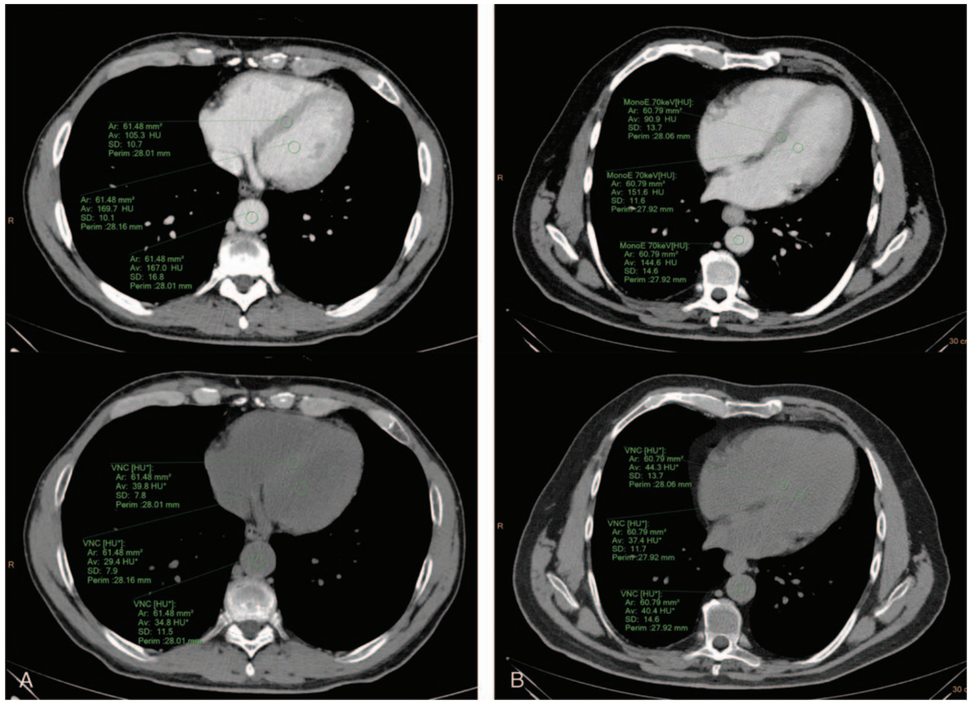

Figure 2. Quantitative image analysis: ROIs placed in the aorta, LV and intraventricular septum in a) patient with anemia and b) a patient without anemia. Note that in case of the patient without anemia the intraventricular septum is not distinctly visible in the VNC-reconstruction and the enhanced conventional image ensures the accurate position of the ROI. ROI = region of interest, LV= left ventricular cavity, VNC = virtual non-contrast.

images in random order to avoid interpretation bias using the vendor's proprietary image viewer (IntelliSpace Portal, v10; Philips Healthcare, Best, the Netherlands). Readers were blinded to clinical (including patients' laboratory findings) and patient data. By using a dichotomous yes or no question, readers were instructed to identify the presence or absence of an hyper-attenuating aortic wall compared to a hypodense aortic blood pool ("aortic ring sign") and the presence or absence hyperdense interventricular septum compared to a relatively hypodense LV cavity ("interventricular septum sign"). To avoid potential interobserver conflicts, patients with equivocal findings were interpreted in consensus as nonanemic. All examinations were evaluated using the common accepted soft tissue standard window settings (window width/level 360/60).[14]

2.4. Quantitative image analysis

For all patients, attenuation (in Hounsfield Units- HU) and standard deviation were assessed by a ROI based method. Circular ROIs of at least 60 mm^2 were placed in the descending thoracic aorta, the intraventricular septum, and the LV cavity in the conventional contrast-enhanced images and copied to the same positions in VNC images (Fig. 2).

Furthermore, the ratio between the CT attenuation of the LV cavity and the interventricular septum was calculated.

2.5. Statistical analysis

R software (version 1.1.456, R development Core Team, R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis. Statistical significance was defined as $P < .05$.

For qualitative analysis, sensitivity and specificity were calculated. Sensitivity was defined as number of true positives / (number of true positives + number of false negatives) and specificity as number of true negatives / (number of true negatives + number of false positives).

For quantitative analysis, correlation between hemoglobin level and measured CT attenuation values in the descending thoracic aorta, the intraventricular septum, and the LV cavity, was determined using linear regression.

Receiver operating characteristic (ROC) curves were generated for quantitative parameters to establish the best diagnostic parameter(s) for predicting anemia on VNC reconstructions. ROC was defined as the two-dimensional graphical approach of the true positive rates against the false positive rates.

Diagnostic performance was determined by calculating the area under the curve (AUC) and the accuracy. The AUC was defined as the average value of sensitivity for all possible values of specificity. Furthermore, for a more precise evaluation of the accuracy, considering both precision and recall, the F1-score was calculated:

$$F1\,score = \frac{true\,positive}{true\,positive + \frac{1}{2}\,(false\,positive + false\,negative)}$$

Interobserver agreement was calculated using the Cohen's kappa coefficient. The interpretation of an agreement was as follows: 0.01–0.2 slight, 0.21–0.4 fair, 0.41–0.6 moderate, 0.61–0.8 substantial, and 0.81–0.99 almost perfect agreement (Landis JR, Koch GG (1977) The Measurement of Observer Agreement

Table 1

Performance of the diagnostic parameters in detecting anemia.

	Specificity	Sensibility	Accuracy	F1-score
Hyperdense aortic sign				
Women and men	98%	42%	70%	0.58
Women	90%	63%	77%	0.72
Men	96%	32%	63%	0.47
Hyperdense intraventricular septum sign				
Women and men	92%	60%	76%	0.71
Women	90%	68%	80%	0.76
Men	93%	54%	73%	0.68
CT attenuation of the left ventricular cavity				
Women and men (<36.5 HU)	68%	74%	71%	0.71
Women (<37.5 HU)	61%	89%	75%	0.77
Men (<36.5 HU)	72%	67%	70%	0.70

CT = computed tomography, HU = hounsfield unit.

for Categorical Data. Biometrics. https://doi.org/10.2307/2529310).

3. Results

3.1. Study population

The study population included 100 patients (60 men; mean age 60.0 ± 13.2 years). Patients' peripheral blood hemoglobin level varied from 6.8 to 15.5 g/dl. Laboratory assessment of hemoglobin values for the anemic group (n = 50) ranged from 6.8 to 12.9 g/dl (mean 10 ± 1.5 g/dl). Corresponding values for the nonanemic group (n = 50) ranged from 12 to 15.5 g/dl (mean 14 ± 0.9 g/dl), $P < .001$.

3.2. Qualitative image analysis

Substantial inter-rater agreement was shown (Cohen's kappa coefficient > 0.6; $P < .01$).

The aortic ring sign showed a slightly higher specificity compared to the interventricular septum sign (98% vs 92%) with both signs yielding a moderate sensitivity of 42% (aortic ring sign) and 60% (intraventricular septum sign). Good accuracy was obtained in both cases: 70% and 76% for the aortic ring sign and intraventricular septum sign, respectively. An overview of the data is shown in Table 1.

In men, the aortic ring sign showed a slightly higher specificity compared to the intraventricular septum sign (96% vs 93%). Accuracy was moderate for the aortic ring sign and good for the intraventricular septum sign: 63% vs 73%. In women, on the other hand, both the aortic ring sign and the interventricular septum sign showed a specificity of 90% and a good accuracy of 77% and 80%, respectively.

Figure 3 shows four examples of analyzed VNC-reconstructions, exemplifying the visualization of both evaluated signs.

3.3. Quantitative image analysis

A positive correlation was found between the hemoglobin level and the CT attenuation values measured in the LV cavity (r = 0.59), the aorta (r = .56), and the ratio between the LV cavity and the intraventricular septum (r = 0.57), respectively (Fig. 4). Weak correlation was shown between the CT attenuation values measured in the intraventricular septum and the hemoglobin levels (r = 0.30).

The ROC curve analysis showed ≤ 36.5 HU (AUC = 0.71) as the best threshold for diagnosing anemia using the LV cavity CT attenuation values. The best threshold for women and men was ≤ 37.5 HU (AUC = 0.75) and ≤ 36.5 HU (AUC = 0.7), respectively. The results of the ROC analysis are shown in Figure 5.

For the determined threshold, the CT attenuation values measured in the LV cavity showed a good sensitivity, accuracy, and F1-score for anemia of 74%, 71% and 0.71, respectively. When considering the sex, a higher sensitivity (89% vs 67%), accuracy (75% vs 70%) and F1-score (0.77 vs 0.7) was shown in women compared to men. An overview of the data is shown in Table 1.

4. Discussion

In this study, we aimed to determine if anemia can be diagnosed on VNC images derived from venous phase scans of SDCT of the thorax and to identify the best subjective, and objective diagnostic parameters to determine anemia in VNC images. The aim of our study was rather to predict anemia in cases where the clinician didn't suspect an anemic state, and therefore sustain the clinician in his daily routine. Thus, patients with acute symptoms or pathologies, as well as patients that had undergone blood transfusions prior to the CT examination have not been included in this study.

The main results of this study were: 1. CT attenuation values in the LV cavity correlated best with the hemoglobin values (r = .59) and showed the best AUC coefficients in the ROC analysis; 2. definition of anemia using the calculated threshold of ≤ 36.5 HU for CT attenuation in the LV cavity showed a sensitivity and accuracy of 74% and 71%, respectively; 3. women showed a much higher sensitivity and slightly better accuracy of 98% and 75%, respectively, with a threshold value of ≤ 37.5 HU; 4. both the aortic ring sign and the intraventricular septum sign showed a high specificity of 98% and 92% and a good accuracy of 70% and 76%, respectively.

Various approaches to detect anemia in unenhanced CT scans have already been described,[4,5,10,11,15] but these methods cannot be applied to enhanced CT examinations. Using high- and low-energy datasets of the polyenergetic x-ray spectra and a SDCT, VNC images can be reconstructed retrospectively by mathematically subtracting iodine from enhanced DLCT images in daily routine. In previous studies, VNC reconstructions provided good results regarding the reliability of iodine

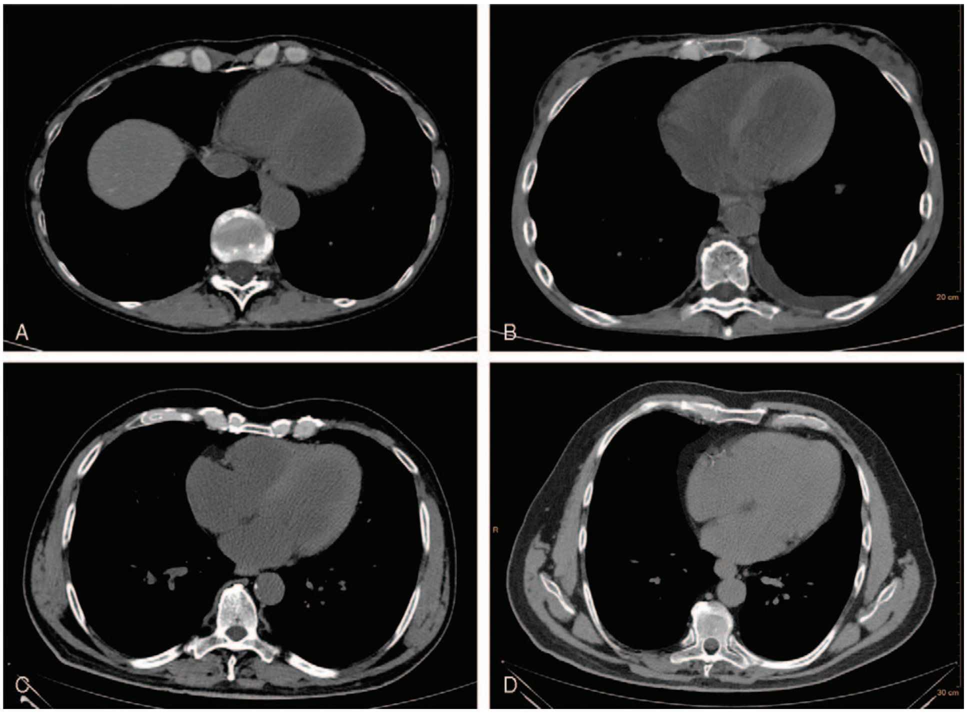

Figure 3. Examples of analyzed VNC-reconstructions showing: A) hyperdense intraventricular septum sign and hyperdense aortic wall sign in a 63-year-old female patient with anemia (Hb 11.5 g/dl). B) hyperdense intraventricular septum sign and hyperdense aortic wall sign in a 56-year-old female patient with anemia (Hb 9.2 g/dl). C) hyperdense intraventricular septum sign in a 70-year-old male patient with anemia (Hb 8.2 g/dl). D) absence of both hyperdense intraventricular septum sign and hyperdense aortic wall sign in a 68-year-old male patient without anemia (Hb 14,7 g/dl). Note that the intraventricular septum is much better visible at lower Hb levels in Figure b) Hb 9.2 mg/dl compared to Figure A) Hb 11.5 mg/dl. Nevertheless, in Figure C) the aortic ring sign is not distinctly visible, although the patient's Hb is 8.2 mg/dl. Legend: VNC = virtual non-contrast, Hb = hemoglobin.

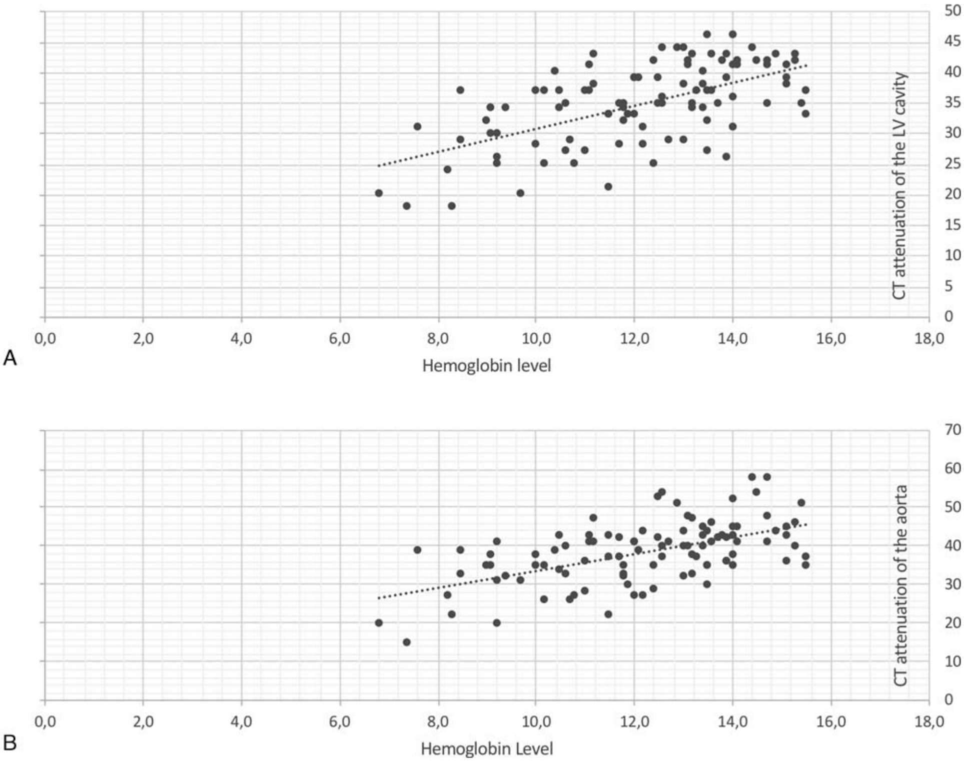

Figure 4. Graphics showing good correlation between Hb level and CT attenuation A) of the LV (r = .59; *P* < .01) and B) of the descending aorta (r = .56; *P* < .01) for all patients and both sexes. CT = computed tomography, Hb = hemoglobin, LV= left ventricular cavity.

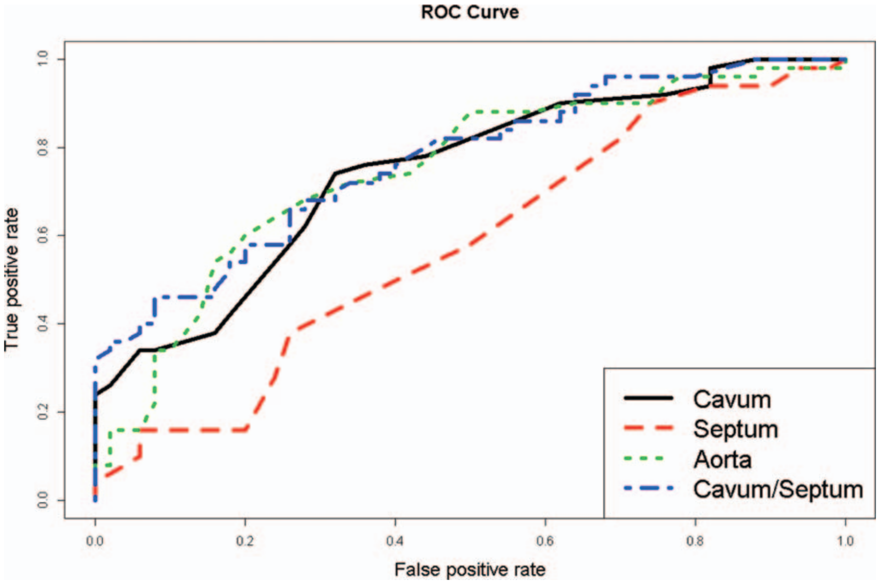

Figure 5. Results of the ROC analysis for the diagnostic parameters: CT attenuation values of the LV 'cavum' (AUC=0.76), the aorta (AUC=0.76), the septum (AUC=0.58) and the ratio between the CT attenuation values of the LV and the intraventricular septum (AUC=0.77). AUC = area under the curve, CT = computed tomography, LV = left ventricular cavity, ROC = receiver operating characteristic.

subtraction and the reproducibility of the HU when compared to unenhanced true non-contrast CT images.[16–19]

Our analysis showed very similar results to the previous studies that analyzed unenhanced CT images, which also described a good correlation between hemoglobin levels and CT attenuation of the LV cavity (r=0.59 vs r=0.55),[5] as well as a similar threshold of ≤ 35 HU for defining anemia.[4,11] One recent study examined the possibility of diagnosing anemia in enhanced CT scans using VNC reconstruction images derived from a novel SDCT.[20] Our study showed also a similar results to this work, both in regards to the correlation between hemoglobin levels and CT attenuation of the blood, and the threshold for defining anemia (r=0.54; HU values of 39.2 and 37.6 for men and women, respectively).[20]

Comparable to previous studies on unenhanced CT images,[5,10] our results showed a weak correlation between hemoglobin values and CT attenuation values of the intraventricular septum (r=0.3).

Contrary to previous studies on unenhanced images, in which for the qualitative analysis the delineation of the intraventricular septum had to be approximated, for example by using different 'helping lines',[5] in our study the ROIs were placed in the contrast enhanced standard images, thus ensuring an exact position of the ROIs (especially in the intraventricular septum), and therefore yielding more reliable results.

To determine the relationship between peripheral blood hemoglobin values and measured HU values, in addition to the calculated linear regression, ROC analysis was performed. For a more accurate assessment, not only AUC and accuracy were calculated, but also the F1-score, so that both precision and recall of the tests were taken into account. Overall, the CT attenuation values in the LV cavity proved to be the best quantitative parameter for the diagnosis of anemia in VNC reconstruction images derived from a novel SDCT.

Qualitative analysis showed high specificity for both the aortic ring sign and the intraventricular septum sign, but both signs showed only moderate sensitivity of 42% and 60%, respectively. The moderate sensitivity can most likely be explained by our strict diagnostic approach, where equivocal findings were interpreted in consensus as nonanemic. Thus, due to the moderate sensitivity, visual analysis of the two signs is not sufficient to rule out anemia and as previously already suggested,[4] quantitative parameters must also be considered.

Our results show a difference between accuracy of predicting anemia in males and females. The interpretation of the observed differences between genders remains a challenging issue. Although different studies describe the gender difference in anemia, which can mostly be explained due to physiological phenomena such as pregnancy, menstruation, but also because of the different mean hemoglobin levels in healthy in venous blood (which might be a direct effect of sex hormones on erythropoiesis), this has to be further analyzed.[21]

Despite its retrospective, single-center setting, this study has a few limitations. First, the sample size of the study was small, therefore, future studies should consider larger sample sizes to validate the results. Second, we have not investigated the cumulative diagnostic value of both quantitative and qualitative parameters, and this issue should further be addressed in the future. Nevertheless, previous studies,[4,11] which evaluated unenhanced images, have indicated that approaching both qualitative and quantitative diagnostic parameters could increase diagnostic certainty.

Our results show that anemia can be diagnosed on VNC images derived from venous phase scans of SDCT of the thorax. As a general approach to reliably predict anemia on VNC images, we propose visual assessment of the presence of the intraventricular septum sign or aortic ring sign, as well as measurement of CT attenuation in the LV cavity (threshold value of ≤ 36.5 HU).

5. Conclusions

In conclusion, predicting anemia in enhanced CT thorax examinations using VNC reconstructions from an SDCT is feasible. A threshold value of ≤ 36.5 HU in the LV cavity was found to be the best definition of anemia. Visualization of the aortic wall or the interventricular septum on VNC images is a specific indicator of anemia. Our results show that anemia can be diagnosed also on contrast enhanced CT images, this offering radiologists the possibility to support clinicians in diagnosing primary asymptomatic anemic patients in daily routine. Further work including a larger number of patients should be considered to validate the current results.

Author contributions

Conceptualization: Andra-Iza Iuga, David Maintz, Tilman Hickethier, Jonas Doerner.
Data curation: Andra-Iza Iuga.
Formal analysis: Liliana Lourenco Caldeira, Jonas Doerner.
Investigation: Lenhard Pennig.
Methodology: Jonas Doerner.
Project administration: Jonas Doerner.
Resources: Jonas Doerner.
Supervision: David Maintz, Jonas Doerner.
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Visualization: Andra-Iza Iuga.
Writing – original draft: Andra-Iza Iuga.
Writing – review & editing: Andra-Iza Iuga, Lenhard Pennig, Liliana Lourenco Caldeira, David Maintz, Tilman Hickethier, Jonas Doerner.

References

[1] Berland LL, Silverman SG, Gore RM, et al. Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee. J Am Coll Radiol 2010;7:754–73.
[2] Morgan L, Choi H, Reid M, Khawaja A, Mazzone PJ. Frequency of incidental findings and subsequent evaluation in low-dose computed tomographic scans for lung cancer screening. Ann Am Thorac Soc 2017;14:1450–6.
[3] Kucharczyk MJ, Menezes RJ, McGregor A, Paul NS, Roberts HC. Assessing the impact of incidental findings in a lung cancer screening study by using low-dose computed tomography. Can Assoc Radiol J 2011;62:141–5.
[4] Kamel EM, Rizzo E, Duchosal MA, et al. Radiological profile of anemia on unenhanced MDCT of the thorax. Eur Radiol 2008;18: 1863–8.
[5] Lan H, Nishihara S, Nishitani H. Accuracy of computed tomography attenuation measurements for diagnosing anemia. Jpn J Radiol 2010; 28:53–7.
[6] Jung C, Groth M, Bley TA, et al. Assessment of anemia during CT pulmonary angiography. Eur J Radiol 2012;81:4196–202.
[7] Doppman JL, Rienmuller R, Lissner J. The visualized interventricular septum on cardiac computed tomography: a clue to the presence of severe anemia. J Comput Assist Tomogr 1981;5:157–60.
[8] Wojtowicz J, Rzymski K, Czarnecki R. Severe anaemia: Its CT findings in the cardiovascular system. Eur J Radiol 1983;3:108–11.
[9] Collins AJ, Gillespie S, Kelly BE. Can computed tomography identify patients with anaemia? Ulster Med J 2001;70:116–8.
[10] Foster M, Nolan RL, Lam M. Prediction of anemia on unenhanced computed tomography of the thorax. Can Assoc Radiol J 2003;54: 26–30.
[11] Title RS, Harper K, Nelson E, Evans T, Tello R. Observer performance in assessing anemia on thoracic CT. Am J Roentgenol 2005;185: 1240–4.
[12] Osipov M, Vazhenin A, Kuznetsova A, Aksenova I, Vazhenina D, Sokolnikov M. PET-CT and occupational exposure in oncological patients. SciMedicine J 2020;2:63–9.
[13] World Health Organization. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity.; 2011. Available at: https://apps.who.int/iris/handle/10665/85839. Accessed March 2020.
[14] Chan O. ABC of Emergency Radiology. 3rd ed. BMJ Books. 2013.
[15] Zhou QQ, Yu YS, Chen YC, et al. Optimal threshold for the diagnosis of anemia severity on unenhanced thoracic CT: a preliminary study. Eur J Radiol 2018;108:236–41.
[16] Toepker M, Moritz T, Krauss B, et al. Virtual non-contrast in second-generation, dual-energy computed tomography: reliability of attenuation values. Eur J Radiol 2012;81:398–405.
[17] Sauter AP, Muenzel D, Dangelmaier J, et al. Dual-layer spectral computed tomography: virtual non-contrast in comparison to true non-contrast images. Eur J Radiol 2018;104:108–14.
[18] Ananthakrishnan L, Rajiah P, Ahn R, et al. Spectral detector CT-derived virtual non-contrast images: comparison of attenuation values with unenhanced CT. Abdom Radiol 2017;42:702–9.
[19] Kahn J, Fehrenbach U, Böning G, et al. Spectral CT in patients with acute thoracoabdominal bleeding-a safe technique to improve diagnostic confidence and reduce dose? Medicine (Baltimore) 2019;98:16101.
[20] Zopfs D, Rinneburger M, Pinto dos Santos D, et al. Evaluating anemia using contrast-enhanced spectral detector CT of the chest in a large cohort of 522 patients. Eur Radiol 2020;31:4350–7.
[21] Murphy WG. The sex difference in haemoglobin levels in adults - mechanisms, causes, and consequences. Blood Rev 2014;28:41–7.