# Development and Clinical Evaluation of a Contrast Optimizer for Contrast-Enhanced CT Imaging of the Liver

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**Objective:** Patient characteristics, iodine injection, and scanning parameters can impact the quality and consistency of contrast enhancement of hepatic parenchyma in CT imaging. Improving the consistency and adequacy of contrast enhancement can enhance diagnostic accuracy and reduce clinical practice variability, with added positive implications for safety and cost-effectiveness in the use of contrast medium. We developed a clinical tool that uses patient attributes (height, weight, sex, age) to predict hepatic enhancement and suggest alternative injection/scanning parameters to optimize the procedure.

**Methods:** The tool was based on a previously validated neural network prediction model that suggested adjustments for patients with predicted insufficient enhancement. We conducted a prospective clinical study in which we tested this tool in 24 patients aiming for a target portal-venous parenchyma CT number of 110 HU ± 10 HU.

**Results:** Out of the 24 patients, 15 received adjustments to their iodine contrast injection parameters, resulting in median reductions of 8.8% in volume and 9.1% in injection rate. The scan delays were reduced by an average of 42.6%. We compared the results with the patients' previous scans and found that the tool improved consistency and reduced the number of underenhanced patients. The median enhancement remained relatively unchanged, but the number of underenhanced patients was reduced by half, and all previously overenhanced patients received enhancement reductions.

**Conclusions:** Our study showed that the proposed patient-informed clinical framework can predict optimal contrast enhancement and suggest empiric injection/scanning parameters to achieve consistent and sufficient contrast enhancement of hepatic parenchyma. The described GUI-based tool can prospectively inform clinical decision-making predicting optimal patient's hepatic parenchyma contrast enhancement. This reduces instances of nondiagnostic/insufficient enhancement in patients.

**Key Words:** computed tomography, contrast agent, hepatic parenchyma, renal cell carcinoma

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Iodinated contrast agents are widely used in CT imaging to enable and improve clinical diagnosis for low contrast tasks.[1] The protocol associated with iodine administration, alongside other scanning parameters such as tube potential and scanning delay, can affect the enhancement within organs and vessels and thus influence the detection of possible abnormalities. However, the iodine contrast itself has also been noted as possible cause of contrast-induced/associated acute kidney injury in patients,[2] as well as allergic reactions including anaphylactic shock.[3] Given the prevalence and importance of iodinated contrast agents, there is a need to ensure that contrast-enhanced CT scans achieve consistent and sufficient enhancement level without overdosing patients with iodine.

Insufficient enhancement may compromise the clinical diagnosis of many irregularities, leading to need for repeat scans[4,5]; likewise, overenhancement may increase the risk of adverse effects and added cost.[3,6–10] One way to achieve consistent and sufficient contrast enhancement is through personalization of the contrast injection/scanning parameters. A recent study, surveying radiologists' preferences on various clinical CT image quality measurements in abdominal CT, indicated the range of clinically acceptable median for hepatic parenchyma portal venous phase HU value to be within 92 to 132 HU.[11] However, achieving such a target for a given patient requires an understanding of the patient's contrast dynamics, so injection/scanning parameters can be personalized on a case-by-case basis.

Multiple prior studies[12–20] have shown correlation between patient attributes and hepatic parenchyma contrast enhancement in contrast-enhanced CT. Such studies offer a pathway to consider personalizing contrast administration to improve the consistency of contrast-enhanced CT image quality. Building on this knowledge, we previously developed a model based on clinical data to predict the magnitude of contrast enhancement of liver CT considering patient attributes (height, weight, age, sex).[21] Tested retrospectively, the study showed the feasibility of having a patient-informed model to predict time-dependent hepatic parenchyma contrast enhancement.[22] To ensure clinical utility, such a model needs to be tested in prospective clinical imaging where an optimized injection/scanning parameters can be enacted in real time.

The purpose of the present study was to develop, implement, and test a clinical contrast-optimizer to support clinical decision-making at the point of care. The optimizer was designed to predict a patient's hepatic parenchyma contrast enhancement prior to the scan and suggest alternative injection/scanning parameters to improve enhancement consistency.

## METHODS

To achieve the purpose of the study, we first developed the enhancement prediction interface and scanning/injection parameters optimizer; then, we preliminary tested the optimizer on prospective contrast-enhanced CT patients. The following sections describe the different phases of study.

### Development of Hepatic Parenchyma Contrast Enhancement Prediction Model

The hepatic parenchyma contrast enhancement prediction was performed using a previously developed hybrid physics/AI-based model.[21,22] The project built an AI model trained on 1577 retrospective contrast-enhanced chest-abdomen-pelvis cases, each with patient attributes (height, weight, age, sex), scanning parameters (tube voltage, injection-to-scan delay), and the iodine contrast administration information (concentration, injection rate, bolus

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**TABLE 1.** Optimization Limits on Different Injection/Scanning Parameters

| Parameter | Optimization Limits |
|---|---|
| Iodine concentration | 300 mgI/mL, 370 mgI/mL, 400 mgI/mL |
| Bolus volume | 50 mL to 200 mL |
| Injection rate | 2 mL/s to 5 mL/s |
| Tube potential | <60 kg: 80–140 kV<br>60 to 135 kg: 100–140 kV<br>>135 kg: 120–140 kV |

The limits were applied to ensure clinical safety and suitable image quality.

volume). The liver parenchyma HU values from these scans were recorded and fitted to a Gaussian function. A two-layered neural network model was trained to predict the parameters of the Gaussian function for given patient attributes and validated on separate retrospective test set yielding a modest prediction accuracy ($R^2 = 0.61$). In preparation for the prospective test, further model validation was conducted using 63 retrospective renal cell carcinoma (RCC) protocol contrast-enhanced scans. This secondary validation study showed a mean overprediction bias of about 1.117 that we subsequently applied as a minor adjustment to the model.

## Development of Optimization Algorithm

Assuming a uniphasic injection protocol, we developed an optimizer to predict the optimal contrast agent administration (injection

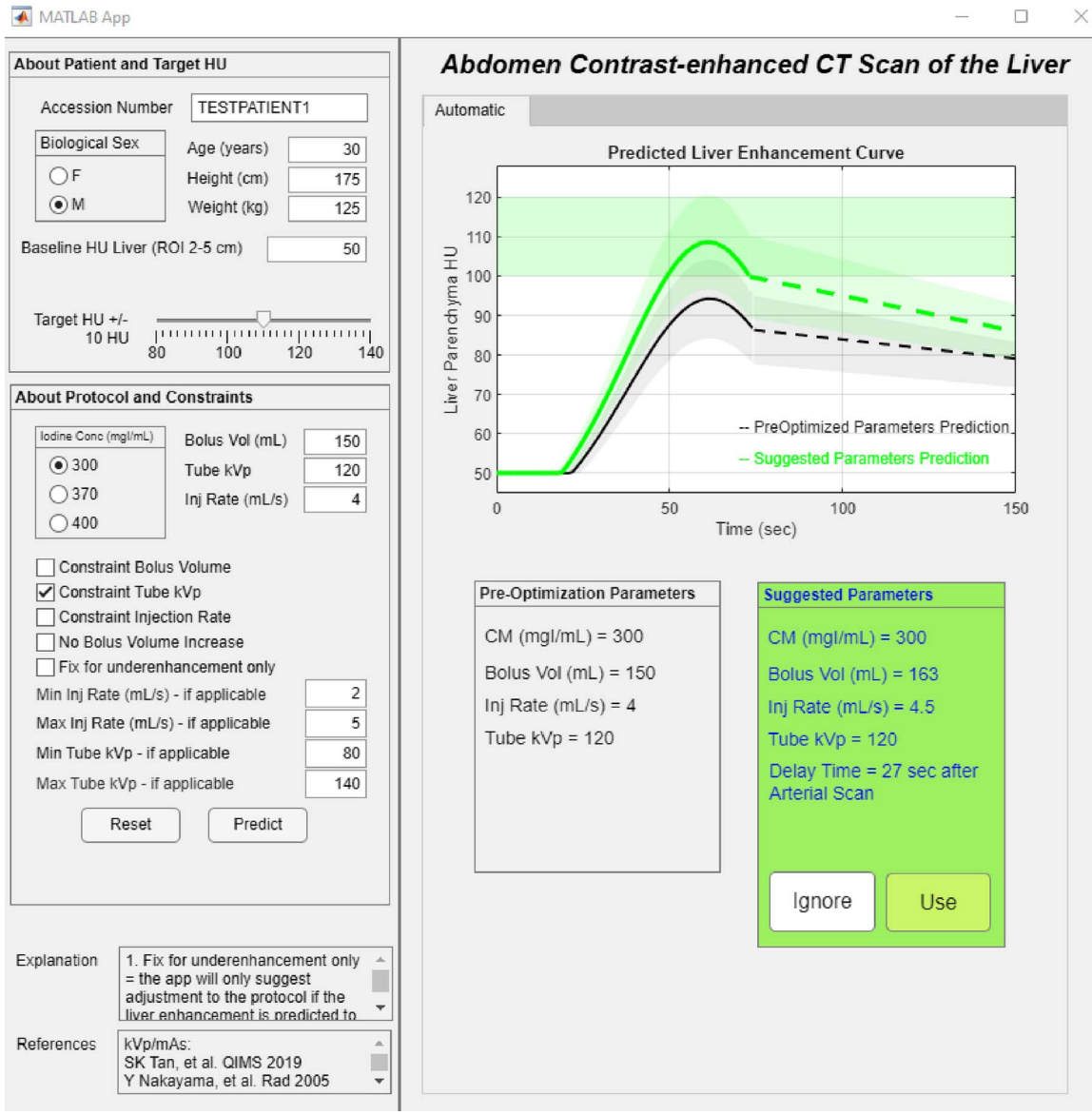


**FIGURE 1.** A screenshot of the GUI of contrast optimizer developed and used in this study. Users would first input all the patient information, desired Target HU for hepatic parenchyma, existing parameters, and any optimization constraints before clicking on the "Predict" button to run the application. A figure on the right-hand side displays the predicted contrast enhancement prediction curves, and two boxes will list the preoptimization and suggested optimized parameters (in green). For this study, CT technologist would then record the action taken (whether the suggested parameters were used or not) by clicking either the "Ignore" or "Use" button, which will save and store all information.

**TABLE 2.** Demographics of Test Patients and the CT Scanner System Used

| Parameter | Test Group Patient Attributes (n = 24) |
|---|---|
| Median age (y) | 71.5 (30–85) |
| Biological sex | 15 Male, 9 female |
| Median height (cm) | 172.9 (144.8–188.0) |
| Median weight (kg) | 85.7 (52.3–158.5) |
| Median BMI (kg/m$^2$) | 29.45 (19.2–45.5) |
| Imaging system | GE Revolution<br>GE Discovery<br>Siemens SOMATOM Definition Flash<br>Siemens SOMATOM Force |

flow rate and total bolus volume) and scanning parameters (tube potential and injection start to scan delay time) aiming to reduce the likelihood of under- or overenhancement (defined as HU values outside the range of target enhancement HU ± 10 HU in this study). The optimizer was developed based on our prior work and informed by previous mathematical pharmacokinetics models and clinical studies.[14,19,23–28] These studies have shown a relatively linear relationship between iodine concentration and the peak enhancement magnitude of the hepatic parenchyma at a given tube potential. Further, the iodine delivery rate is the primary indicator of the enhancement peak time: the higher the injection rate, the earlier the peak (assuming constant bolus volume). Using the difference between the predicted peak enhancement level and the target enhancement value, the algorithm was designed to calculate the amount of adjustment needed of each included parameter (tube potential, bolus volume, and injection rate) to achieve the targeted enhancement. In consultation with radiologists and technologists, to prevent drastic changes to any individual parameters, we incorporated the safety limits of the optimization parameters listed in Table 1 into the optimizer algorithm.

Whereas our prediction model originally predicts scan delay from the start of the injection, the bolus tracking process used in the RCC protocol (Fig. 1) introduces uncertainty in scan delay time, as the image acquisition will not trigger unless certain aortic enhancement threshold is reached (150 HU). Multiple factors, including the size and location of the bolus tracking ROI, may affect the mean enhancement HU used to determine whether the aorta has reached the preset threshold. As such, we assumed a 40-second delay between start of injection and the arterial phase. For example, if the model predicts a contrast enhancement peak around 75 seconds, the displayed suggested arterial-to-portal venous scan delay would be 35 seconds. In addition, we limited the optimization of the arterial-to-portal venous phase delay to 25 to 45 seconds, consistent with current clinical expectations.

We added a weight-based limitation on the minimum tube potential used, ranging from 80 kV for patients <60 kg to 120 kV for patients >135 kg, while allowing a provision to maintain the kV value as prescribed. Further, whereas cardio-focused protocols regularly use injection rate of more than 5 mL/s, the maximum injection rate for this study's scan protocol was set to 5 mL/s to reduce extravasation rate and discomfort.

## Development of the Prediction-Optimization Graphical User Interface Tool

In the second phase of the study, we combined the prediction model and the optimization algorithm in a graphical user interface (GUI) (Fig. 1) to create a user-friendly interface, which allows for interactivity and display of prediction and suggested protocol for a given patient. Editable fields enabled users to input patient attribute information (height, weight, age, sex), the baseline hepatic parenchyma HU value, and the default injection/scanning parameters (bolus volume, tube potential, injection rate). Additional buttons and check boxes were used to display sex and iodine concentration choices. The user could include any clinical limitations, such as maximum/minimum parameter values, and keep certain parameter (s) unchanged. The target enhancement value could be changed by sliding the Target HU slider; otherwise, the default was set to 110 HU.

Based on the information provided, the optimizer would predict if the default protocol would lead to the peak enhancement to fall outside the target range. If so, the optimizer would suggest alternative parameters to achieve an enhancement within the targeted range. The patient information, prediction, optimization choices, and parameters would be saved in a text file for analysis. In addition, a simple display of the prediction contrast enhancement curves, using both standard parameters and suggested parameters, was made available by the interface.

## Clinical Test Patient Selection

This work was performed in compliance with HIPAA and was determined to be exempt from the institutional review board requirements. CT images were acquired from 24 patients (test group) who were scanned using RCC protocol at the BLIND hospital in January 2023. Exclusion criteria were applied to no-show patients and patients with >2 mg/mL creatinine level, a contraindication for iodine usage, or those with iodine allergy that did not take their steroid/anti-allergy medications. Patient demographics are displayed in Table 2. Patient information, such as height, weight, BMI, age, and biological sex, were acquired from their electronic health record. Out of the 24 consecutive patients included in the study, 19 had prior RCC or similarly protocoled contrast-enhanced abdominal CT scans, ranging from 2 months to 1 year prior to January 2023. We used the previous scans as benchmark, assuming minimal intrapatient variation between scans. Standard RCC protocol calls for an injection of either 150 mL of 300 mgI/mL iodine contrast at 4 mL/s rate or 125 mL of 370 mgI/mL iodine contrast at 3.3 mL/s. The iodine contrast medium used was ISOVUE (Bracco Diagnostics, Monroe Township, NJ).

To rule out the possibility of coincidence or chance affecting the results, we conducted a comparison between the test group and a control group. The control group consisted of 25 retrospective patients with similar median BMI who also underwent two RCC scans, more recently in late February 2023/early March 2023, and one previously between 1 month and 16 months prior, but without any optimization. Table 3 displays the demographics of the control patient.

**TABLE 3.** Demographics of the Control Group Patients and the CT Scanner System Used

| Parameter | Control Group Patient Attributes (n = 25) |
|---|---|
| Median age (y) | 65 (46–80) |
| Biological sex | 19 Male, 6 female |
| Median height (cm) | 175.0 (154.9–195.6) |
| Median weight (kg) | 86.0 (65.7–156.0) |
| Median BMI (kg/m$^2$) | 28.8 (22.5–53.9) |
| Imaging system | GE Revolution<br>GE Discovery<br>Siemens SOMATOM Definition Flash<br>Siemens SOMATOM Force |

## Image Acquisition and Processing

The 24 test group patients were equally divided between scanners from two major CT manufactures (GE Healthcare, Waukesha, WI, and Siemens Healthineers, Forchheim, Germany). Automated tube current modulation was enabled for all the CT systems. Figure 2 illustrates the standard and the optimized RCC protocols. The standard RCC protocol consists of imaging prior to iodine injection, an initial delay of 9 seconds after the injection starts, followed by continuous monitoring scans every 2 to 3 seconds until the aorta reaches 150 HU, a 12-second delay before the arterial phase scan, and another 45-second delay prior to the final portal venous phase scan. Standard default clinical practice recommends tube voltage of 140 kV for patient with BMI >30 kg/m$^2$ and 120 kV for BMI <30 kg/m$^2$.

At the beginning of each scan, the CT technologist entered the patient information and the default scanning/injection parameters. After the noncontrast scan was acquired, the technologist drew a 2- to 3-cm diameter circular ROI in a uniform part of the hepatic parenchyma, avoiding any visible vessel or abnormalities, and recorded the mean CT number of the ROI in the GUI. Then, the GUI predicted and displayed the hepatic parenchyma contrast enhancement curve. If the liver was predicted to achieve proper enhancement, no alternative parameters were suggested. Otherwise, new parameters were suggested, excluding alternatives to any parameters that were opted out by the technologist from the optimization. The CT technologist would have the option to adjust the necessary parameters, suggested by the GUI, or decline to use the suggestions for any reason.

Postacquisition, the outcome was evaluated by assessing the final hepatic parenchyma HU value of the portal venous imaging for each patient. This was done manually by placing three ROIs in the hepatic parenchyma, avoiding any visible vessel or abnormalities, and averaging the three values together. Nineteen of the 24 test patients in this study had a prior RCC or similar scan, and as such, the measurements of these 19 patients were also compared with contrast-enhanced abdominal CT scans of the same patients acquired at an earlier date with the standard RCC protocol.

## Statistical Test

Coefficients of variation (CVs) were calculated to compare the hepatic parenchyma enhancement of test group patients with their respective prior RCC or similarly protocoled abdominal contrast-enhanced CT scans of the portal venous phase. If there was a mismatch of tube potential kV between the scan comparison, the enhancement level of the earlier scan was rescaled linearly using coefficient found in Ref. 14. Given the size and the non-Gaussian nature of these data sets, the Ansari-Bradley test was used to determine whether the change in dispersion/consistency was statistically significant. Similarly, CVs and Ansari-Bradley test were calculated for the control group of 25 retrospective patients receiving no optimization in either their earlier or later RCC scans.

# RESULTS

The GUI took <1 second to predict and suggest alternative protocol, if applicable. Figure 3 illustrates the changes made to the parameters for each patient. Overall, 15 test patients received adjustments to their injection protocol (bolus volume and injection rate), and all test patients received adjustment to their scanning delay between the arterial scan and the portal venous phase scan. No technologist deemed to use the provision for kV adjustment. For the patients receiving injection protocol adjustments, the median adjustments were 8.8% bolus volume reduction and a 9.1% injection rate reduction. All test patients were scanned about 42.6% earlier than the typical 45-second scanning delay they would have received. Most test patients had their delay reduced to 25 seconds, which was also the minimum limit we set for the adjustment. However, without this floor, 18 of the 24 test patients would have received even shorter delays, ranging from

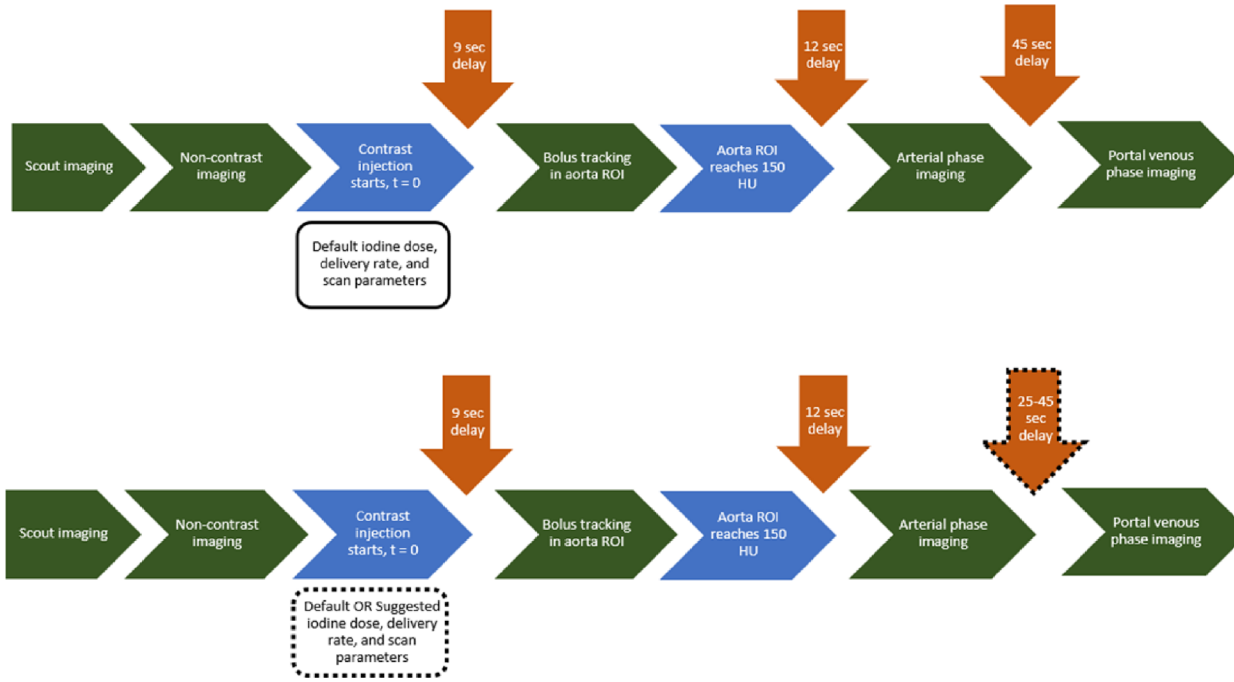


**FIGURE 2.** (Top) Standard renal cell carcinoma (RCC) contrast-enhanced CT imaging protocol. (Bottom) Optimized RCC CT imaging protocol with alternative injection/scanning parameters used. Green color indicates different stages of image acquisition, whereas blue indicates timing milestones. Orange arrows indicate the delay between phases.

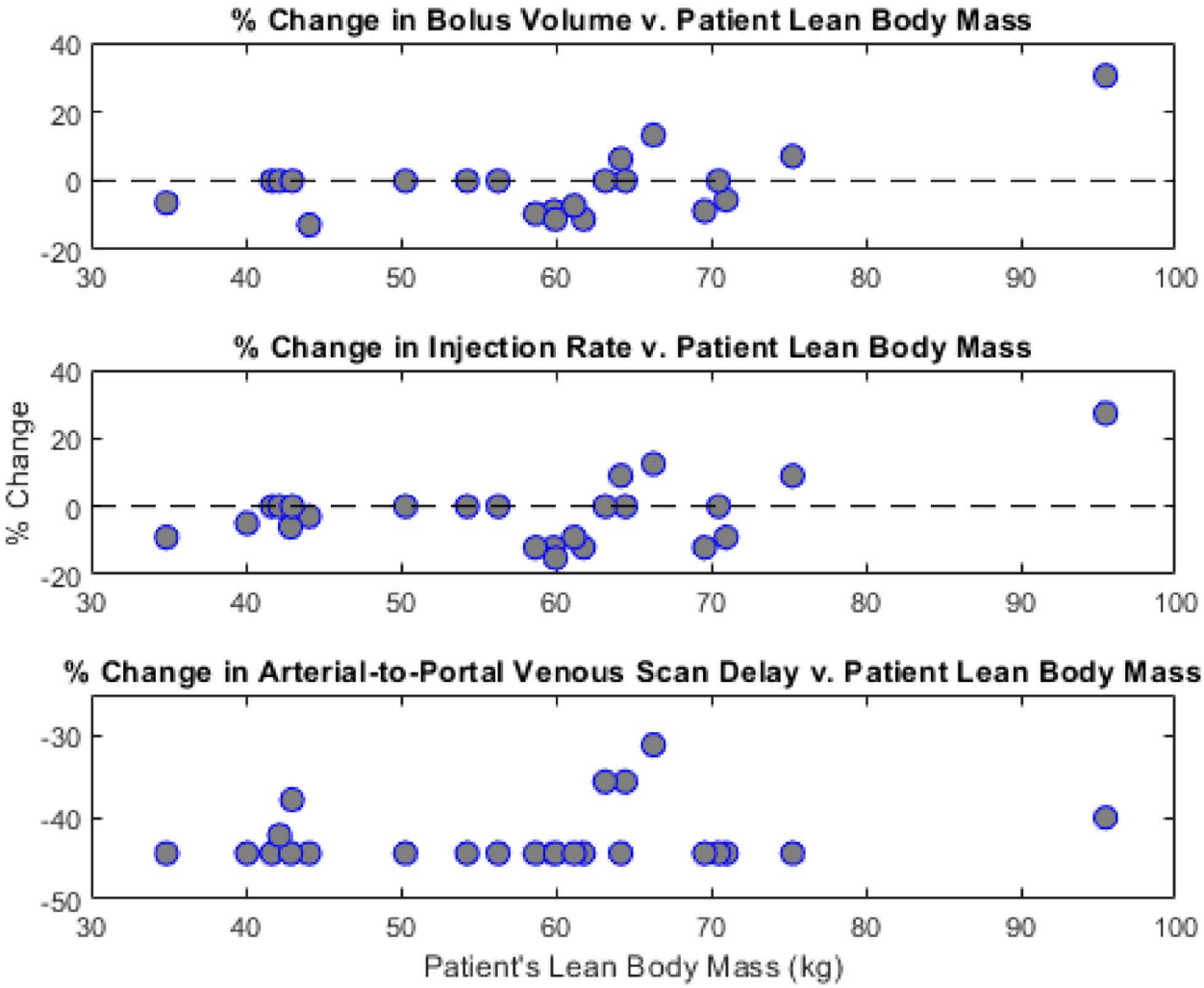


**FIGURE 3.** Scatter plots of the adjustment (% change) from the conventional parameters made to each of the 24 test patients' bolus volume, injection rate, and arterial-to-portal venous phase scan delay. The % change adjustment is plotted against the respective patient's lean body mass (kg).

18 to 24 seconds. This translates to a reduction of the median total delay time between the start of injection and the portal venous phase scan of 68 to 95 seconds.

Figures 4 demonstrates the outcomes of each patient in comparison with their previous scan (if available), alongside their lean body mass (LBM) estimation using the Boer formula.[29] Results show hepatic parenchyma HU consistency improvement with a CV of 0.11 compared with 0.21 achieved by the retrospective scans. The median HUs for the two groups were similar (111.3 HU vs 108.7 HU). The number of underenhanced test patients was halved, and all previously overenhanced test patients received enhancement reductions. The performed statistical test rejected the null hypothesis ($P = 0.012$), indicating an unequal variance between the two scan groups. In addition, the control group's CV for the earlier scan was 0.17 and, for the more recent scan, was 0.16 with median values of 110.1 HU and 109.3 HU (Fig. 5), respectively. Despite the difference in CV, the performed statistical test failed to reject the null hypothesis ($P = 0.67$), indicating insignificant variance difference of the two scan groups. The overall distribution of HU values in the two groups is illustrated in Figure 5, and an example optimization case is demonstrated in Figure 6.

## DISCUSSION

We demonstrated the feasibility of using a clinical GUI-based tool to prospectively predict a patient's hepatic parenchyma contrast enhancement and subsequently suggest personalization of the injection/scanning parameters to minimize the likelihood of under- and overenhancement. Whereas other studies have conducted weight-based consideration[30,31] or used mathematical modeling[32] to adjust the injection or scanning parameters, to our knowledge, ours is the first to prospectively personalize such parameters using a real-time patient-informed machine learning prediction model.

In our previous retrospective study, we showed that a hepatic parenchyma enhancement prediction could potentially identify 84% of underenhanced cases and half of overenhanced cases.[21,22] This allows for certain optimization adjustments to be made to reduce the chance of improper enhancement. Our present prospective study results agreed with our previous assessments; of the 19 test patients with previous scans, 7 had enhancement values under 100 HU and 8 above 120 HU. We were able to improve the enhancement level in all 7 underenhanced patients and reduce the

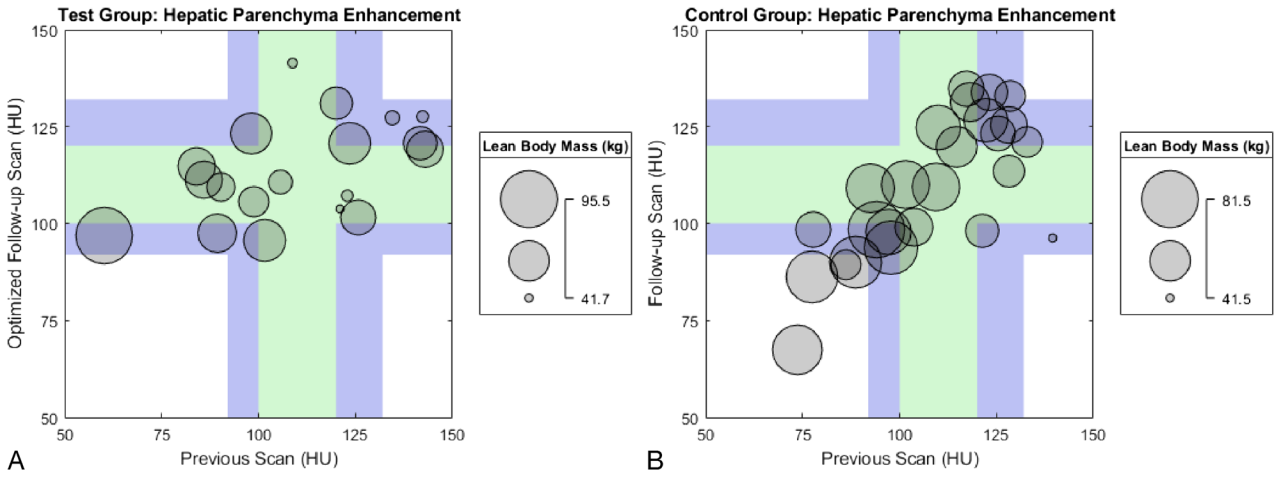


**FIGURE 4.** (Left) Scatter plot of the outcome of the test group patient study scans (in HU) in comparison with previous scan (if applicable) of each patient. Only 19 of the 24 test group patients have received RCC or abdominal protocol contrast-enhanced CT imaging at our institution. (Right) Scatter plot of the outcome of the control group patient scans (in HU) between an earlier RCC-protocoled scan with a more recent follow-up scan of the same protocol for each patient. None of the scans received any optimization. The size of the bubble is linearly proportional to the lean body mass of the patient. The green shaded area represents the radiologist-preferred target range for hepatic parenchyma enhancement in this study (100 < HU < 120), whereas the blue-shaded region represents the target enhancement range according to the study of Cheng et al.[11]

enhancement level for all 8 overenhanced patients. This resulted in an improved consistency of enhancement across test group patients and the reduction of test patients getting nondiagnostic, insufficient enhancement, as demonstrated by the reduction of the CV from 0.21 to 0.11 and a median value close to the target enhancement value of 111.0 HU (Fig. 6). Further, the statistical test of the control group (Figs. 5 and 6) suggests that the observed consistency improvement in the test group is unlikely to be due to chance.

Test patients with higher BMI/LBM values received a suggested higher iodine delivery rate as compared to those with lower BMI/LBM, who typically receive a reduction in both the delivery rate and bolus volume. This is consistent with our previous

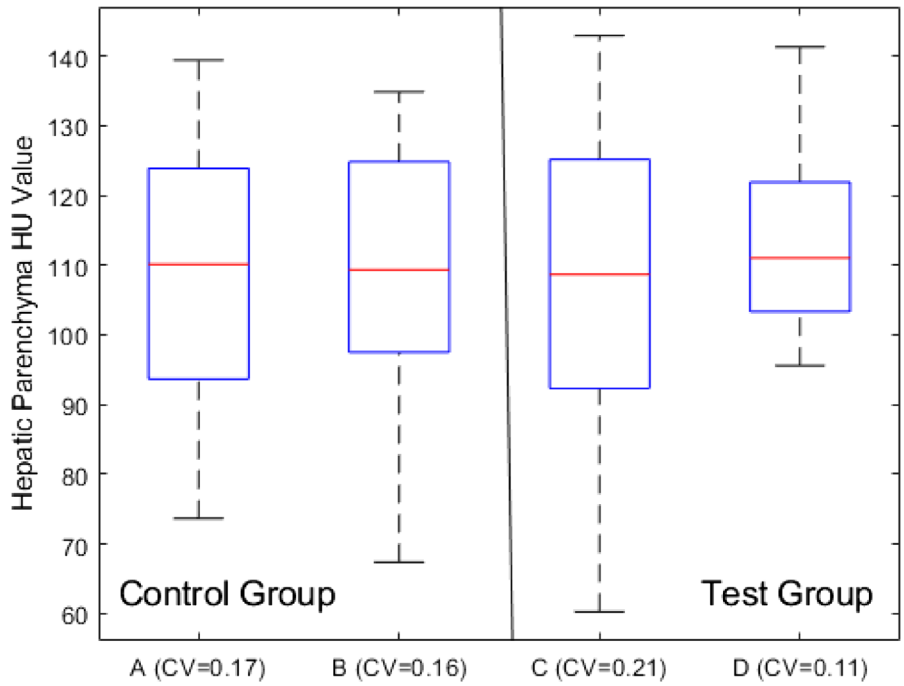


**FIGURE 5.** A comparison of the enhancement outcome of the hepatic parenchyma at portal venous phase between the control group (left) and the test group (right). RCC-protocoled scans in control group A were conducted between September 2021 and January 2023, whereas scans in group B (of the same patients) were done in late February 2023 and early March 2023. The control group patients did not receive any optimization in either scan. RCC-protocoled scans in group C were acquired between June 2020 and November 2022, whereas scans in group D were acquired in late January 2023 and early February 2023. Scans in group D underwent optimization, whereas scans in group C (of the same patients as group D) did not receive optimization. Coefficient of variations are displayed in the legend.

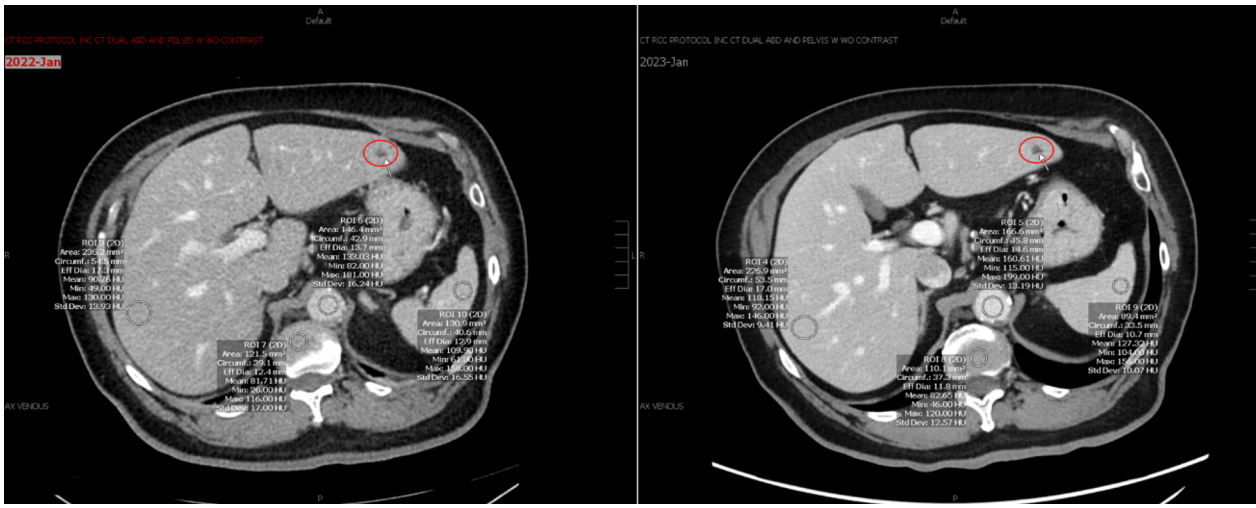


**FIGURE 6.** A comparison of a patient's scan from January 2022 (without optimization) and January 2023 (with optimization). Both scans display a hypo-attenuating lesion on the lateral segment of the liver left lobe (red circle). The newer scan has a higher contrast resolution and therefore better identification of the lesion's margins. The lesion also appears less heterogeneous.

finding that contrast enhancement in hepatic parenchyma is inversely correlated with patients' weight. In addition, despite cutting the average delay time by 20 seconds, the test patients still achieved proper, in many cases higher, enhancement level as compared to their previous scans. This confirms that the liver contrast enhancement peak time for scans with similar injection parameters used in our study typically happens earlier than the 96 seconds median scan injection-to-portal venous delay used in the original RCC scanning protocol.

The ability to reduce the amount of contrast iodine used and to shorten the scan delay can not only improve enhancement consistency but potentially reduce the rate of contrast-induced adverse effect and lower the operational cost. The cost-saving effect is somewhat limited given the current common clinical practice of discarding unused contrast iodine after each patient scan. However, reduction of iodine use may translate to savings of iodine if the practice could allow multiple draws from the same contrast source.

There are limitations to this study. Whereas our optimization primarily focuses on achieving a certain contrast enhancement value, future studies may consider optimizing a more task-based image quality metric, such as the detectability index, d′.[33,34] Using this metric, contrast media administration, resulting image quality, and radiation exposure can all be a part of a comprehensive optimization process. For instance, the software would prioritize less bolus volume for patients with known iodine allergy or compromised kidney function, whereas the priority for younger patients would be to reduce radiation exposure — all while maintaining a certain target d′ value.[35] Second, the current clinical practice does not allow for personalization by selecting contrast iodine concentration. Future ability to customize iodine concentration for each patient would complement our effort to deliver a personalized protocol to ensure enhancement sufficiency. Finally, the number of patients we used for the study's clinical testing part was limited, and none had reported cirrhosis. Cirrhosis causes disruption in the liver blood flow, potentially affecting contrast enhancement/perfusion dynamics. Many studies have reported the peak enhancement of hepatic parenchyma in cirrhotic liver to be lower than that of normal liver.[27,36] Although we are actively conducting an exploratory study to confirm this trend, the result is still too preliminary to be included here.

In conclusion, we developed and preliminarily tested a patient-informed clinical framework that predicts contrast enhancement of a patient's hepatic parenchyma and suggests empiric injection practices and scanning parameters when enhancement is predicted to be suboptimal. The test in 24 patients improved the hepatic parenchyma contrast enhancement consistency and decreased the number of underenhanced patients as compared to their previous scans, demonstrating the tool's potential benefit if implemented in clinical practice.

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