Modeling Patient-Informed Liver Contrast Perfusion in Contrast-enhanced Computed Tomography

Hananiel Setiawan, BS,† Francesco Ria, DMP,* Ehsan Abadi, PhD,* Wanyi Fu, MS,*‡ Taylor B. Smith, BS,*† and Ehsan Samei, PhD*†‡*

Objective: To determine the correlation between patient attributes and contrast enhancement in liver parenchyma and demonstrate the potential for patient-informed prediction and optimization of contrast enhancement in liver imaging.

Methods: The study included 418 chest/abdomen/pelvis computed tomography scans, with 75% to 25% training-testing split. Two regression models were built to predict liver parenchyma contrast enhancement over time: first model (model A) utilized patient attributes (height, weight, sex, age, bolus volume, injection rate, scan times, body mass index, lean body mass) and bolus-tracking data. A second model (model B) only used the patient attributes. Pearson coefficient was used to assess predictive accuracy.

Results: Weight- and height-related features were found to be statistically significant predictors ($P < 0.05$), weight being the strongest. Of the 2 models, model A ($r^2 = 0.75$) showed greater accuracy than model B ($r^2 = 0.42$).

Conclusions: Patient attributes can be used to build prediction model for liver parenchyma contrast enhancement. The model can have utility in optimization and improved consistency in contrast-enhanced liver imaging.

Key Words: contrast enhancement, prediction, liver

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More than half of clinical computed tomography (CT) imaging in the United States involves the use of iodinated contrast materials.[1] The use of such contrast agents in CT imaging enhances tissue contrast, particularly in soft tissue organs, such as the liver, pancreas, spleen, and kidneys, and thus improves the depiction of a variety of disorders. Despite the critical role of contrast media administration in clinical practice, there is a lack of standardization in contrast administration techniques across institutions; for instance, a common approach is to use the same dose and injection rate in every patient, whereas others make slight adjustment based on patient weight thresholds.[2,3] As a result, many studies have indicated inconsistencies in contrast enhancement across different patients, posing clinical diagnostic risk in overenhanced and underenhanced patient cases.[4] There is a need to devise optimal and standard contrast media administration procedures to target clinically adequate organ contrast enhancement to target consistent diagnostic performance and to minimize and adjust the magnitude of contrast administration per patient specifics.

This need can be approached by building a model that prospectively characterizes contrast media perfusion and contrast enhancement per patient characteristics. Previous studies have indicated that contrast enhancement is correlated with patient weight and other body habitus metrics (ie, body mass index [BMI] and lean body mass [LBM]),[5–14] the variability of which across patients leads to variability in organ enhancements. However, the existing models rely primarily on mathematical pharmacokinetics modeling and are not individualized to patient-specific attributes, scanning parameters, and contrast media administration techniques. One of these models, the physiology-based pharmacokinetics (PBPK) model[15,16] is a compartmentalized, differential-equation based model which predicts contrast enhancements in different organ as a function of injection time for an averaged population. Although the result of the PBPK model has been shown to be in agreement with averages across cases,[16] it does not provide sufficient individualization to patient-specific attributes.[17] To reduce inconsistencies in contrast enhancement in the clinic, there is a need to build a contrast perfusion model that incorporates patient-specific attributes.

This study had 3 purposes[1]: to investigate the correlations between known pre-scan patient attributes, such as weight, height, and age, with contrast enhancement in liver over time in clinical patient populations,[2] to develop a patient-informed, machine learning-based time-dependent contrast enhancement prediction model based on these correlations, and[3] to theoretically demonstrate the potential clinical benefit of using such model to inform contrast administration protocol.

MATERIALS AND METHODS

Patient Library and Data Sources

This Institutional Review Board-approved retrospective study included 418 adult patients (210 female) who underwent chest/abdomen/pelvis CT examinations with iodinated contrast performed with tube current modulation in 2018 at Duke University Medical Center. For each examination, patient's attributes (height, weight, age, and biological sex), scanner parameters (CT vendor/type, tube potential, slice thickness, scan times), as well contrast administration protocol (bolus volume, concentration, flow rate, injection duration) were collected using a quality and safety patient information system (METIS, Duke University) and a contrast management system (NEXO; Bracco Diagnostic Inc., Monroe Township, NJ). Considering a previous study which shows correlation between LBM and contrast enhancement,[9] the LBM of each patient was calculated using the Boer formula based on patients' height and weight.[18] For each case, contrast media was injected using a uniphasic injection protocol for iodine-based contrast agent with concentration of 300 mgI/mL. In addition, the CT scanning examination included a bolus tracking contrast monitoring series to determine the appropriate scan start time; these images were repetitively acquired every 3 seconds, starting

From the *Carl E. Ravin Advanced Imaging Laboratories, Department of Radiology, †Graduate Program in Medical Physics, School of Medicine, and ‡Department of Electrical and Computer Engineering, Pratt School of Engineering, Duke University, Durham, NC.

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Correspondence to: Hananiel Setiawan, 2424 Erwin Rd, Ste. 302, Durham, NC 27705(e-mail: hananiel.setiawan@duke.edu).

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TABLE 1. Summary of Patient Attributes and Contrast Administration

	Mean	Median	Range [Min, Max]	Std. Dev.
Height, cm	170.1	170.2	[135.9, 195.8]	10.2
Weight, kg	84.9	83.9	[49.0, 137.9]	17.9
BMI, kg/m^2	29.5	28.8	[18.0, 52.8]	6.4
LBM, kg	48.2	44.6	[27.6, 72.9]	10.8
Age, y	59.1	61.0	[19.0, 94.0]	15.0
Contrast bolus volume, mL	145.6	146.0	[136.0, 154.0]	2.5
Average injection rate, mL/s	2.9	2.9	[2.0, 3.0]	0.1
Start-of-injection to scan duration interval, s	69.2	69.0	[54.0, 98.0]	7.6

from 45 seconds postinjection, to monitor whether the organ of interest has received proper contrast enhancement before the diagnostic scan commences. The summary of this dataset is provided in Table 1 and Table 2.

Image Segmentation

Each patient case included 3 types of data: (1) premonitoring image, taken before contrast injection starts; (2) monitoring images, taken as contrast was being injected during the bolus tracking period; and 3) diagnostic image series. The livers were automatically segmented in the CT images using a deep learning-based algorithm.[19] This segmentation tool, previously trained on 200 CT images manually segmented by radiologist experts, is able to identify major body organs, including liver, with dice similarity coefficient values greater than 0.85. The median HU value of the segmented livers was used to represent the enhancement value.

Model Development

The correlation between the patient attributes and contrast enhancement was evaluated in terms of Pearson correlation coefficient. Using the correlation and relationship between contrast enhancement in the liver and the patient attributes (height, weight, age, sex), linear regression (MATLAB) were used to build 2 liver contrast enhancement prediction models. Seventy-five percent of the total cases were used to train the models, and the rest were used for testing. Both models were evaluated using a 5-fold cross validation strategy. The features used for training included height, weight, sex, age, bolus volume, injection rate, scan times, calculated BMI, and calculated LBM.

Two models were developed; in the first model (model A), the monitoring scan data were used as additional input, whereas the second model (model B) predict contrast enhancement at diagnostic time without the monitoring data. The training outcome was set to be the contrast enhancement in Hounsfield Unit (HU). The goodness of fit was evaluated in terms of R,^{2} mean absolute error, and mean squared error. We also compared our result with the result of the PBPK model.

Demonstration of Clinical Implication

To illustrate the potential benefit of implementing a predictive model to adjust contrast administration protocol, we used the Model A to retrospectively predict the HU value of the organ at time-of-scan. We then theoretically adjusted the contrast media concentration, assuming simple linearity between contrast media concentration and organ contrast enhancement,[14] such that the parenchyma enhancement HU level is within the median clinically acceptable range of 92 to 132 HU.[20] We compared the consistency of the parenchyma enhancement level in our patient cases before and after the application of this predictive model.

RESULTS

Correlations of Different Attributes to Contrast Enhancement

The Pearson correlation coefficients between the different patient attributes (weight, BMI, LBM, height, and age) are shown in Table 3. Patient weight had the strongest correlation with contrast enhancement over time, while age did not have statistically meaningful correlation. Weight-derivative features, such as BMI and LBM, have weaker correlations compared with that of patient weight. In general, we found patient weight and other weight-related features to be inversely correlated with contrast enhancement. In addition, we observed the correlations between these patient attributes and contrast enhancement varied over time.

Prediction Models

Figure 1 shows the plots of the predicted versus the actual contrast enhancement along with the 1:1 line and the error probability density function for model A, Figure 2 refers to model B, and Figure 3 refers to the PBPK model. The 2 regression models perform better than the PBPK model as demonstrated by the R^2 values, as shown in Table 4. The inclusion of contrast monitoring data also improves the predictive accuracy of the model; in our case, the R^2 value increases from 0.42 to 0.75 when contrast monitoring data are used to train the model.

Clinical Implication

Among the patient cases we use in this study, we found 17% of the patients from our library were underenhanced (<92 HU), whereas 19% were overenhanced (>132 HU) during their diagnostic scans. Using model A to theoretically and retrospectively adjust the concentration of contrast media reduces the interquartile range of liver enhancement across patients by 60% compared with actual levels of enhancement, as shown by Figure 4.

DISCUSSION

Variabilities in patient attributes and body habitus can greatly affect organ contrast enhancement in contrast-enhanced CT imaging. Despite this, the practice of contrast administration does not consider such factors and is often different across institutions. This results in inconsistencies in organ contrast enhancement and exposes

TABLE 2. Summary of Examinations Included in the Study by Clinical Protocols, Scanners, and Scan Parameters; Noise Index (NI) for GE Healthcare Scanners; Reference Effective mAs (Q) for Siemens Healthineers Scanners

Institution	Vendor	Models	Slice Thickness, mm	NI, Q	kV	Pitch
Duke University Medical Center	Siemens Healthineers	SOMATOM Definition Flash, Force	0.6	150, 200	120	0.8
	GE Healthcare	Discovery CT750HD, Revolution, VCT	0.625	19.2, 22.0	120	1.38

TABLE 3. Correlation Between the Patient Attribute Features With Contrast Enhancement

	45–50 Seconds				50–55 Seconds				55–60 Seconds			
Features	***r***	***P***	**95% LL**	**95% UL**	***r***	***P***	**95% LL**	**95% UL**	***r***	***P***	**95% LL**	**95% UL**
Weight	−0.19	3.20E-03	−0.31	−0.07	−0.23	4.22E-04	−0.35	−0.11	−0.31	1.55E-06	−0.42	−0.19
BMI	−0.11	**8.85E-02**	−0.24	0.02	−0.13	4.93E-02	−0.26	−4E-04	−0.20	1.90E-03	−0.33	−0.08
LBM	−0.22	6.90E-04	−0.34	−0.10	−0.24	2.22E-04	−0.36	−0.12	−0.31	1.45E-06	−0.43	−0.19
Height	−0.17	1.19E-02	−0.29	0.04	−0.19	4.30E-03	−0.31	−0.06	−0.19	3.60E-03	−0.31	−0.06
Age	0.01	**8.21E-01**	−0.11	0.14	−0.07	**3.09E-01**	−0.20	0.06	−0.12	**6.19E-02**	−0.25	0.01
	60–65 s				65–70 s				70–80 s			
Features	***r***	***P***	**95% LL**	**95% UL**	***r***	***P***	**95% LL**	**95% UL**	***r***	***P***	**95% LL**	**95% UL**
Weight	−0.33	8.65E-06	−0.46	−0.19	−0.42	2.01E-06	−0.56	−0.26	−0.43	5.88E-06	−0.58	−0.26
BMI	−0.20	8.70E-03	−0.34	−0.05	−0.34	1.56E-04	−0.49	−0.17	−0.40	4.21E-05	−0.55	−0.22
LBM	−0.36	2.00E-06	−0.48	−0.22	−0.32	3.41E-04	−0.47	−0.15	−0.30	2.50E-03	−0.47	−0.11
Height	−0.22	3.50E-03	−0.36	−0.08	−0.12	**1.80E-01**	−0.30	0.06	−0.08	**4.42E-01**	−0.27	0.12
Age	−0.04	**6.36E-01**	−0.19	0.11	0.05	**5.78E-01**	−0.13	0.23	0.13	**1.80E-01**	−0.06	0.32

P values below 0.05 are highlighted in bold.

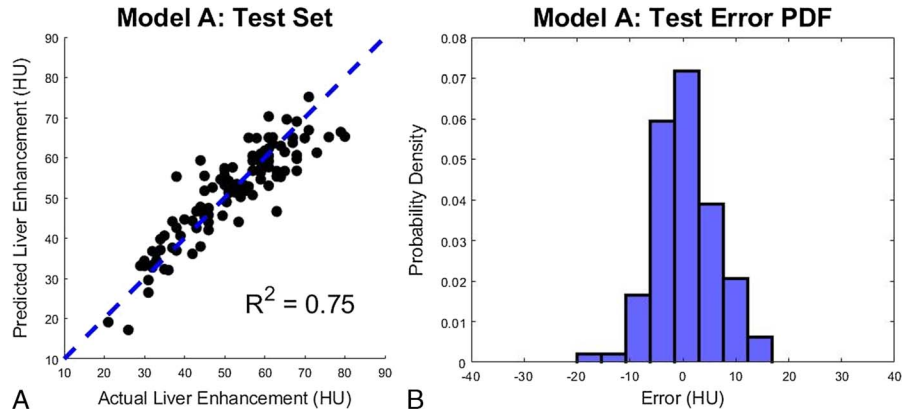

FIGURE 1. A, Scatter plot of the predictions vs actual HU values of test set for Model A (includes monitoring data). The red line shows the perfect prediction, 1:1 line. B, Error partial distribution function (predictions–actual) of the prediction. Figure 1 can be viewed online in color at www.jcat.org.

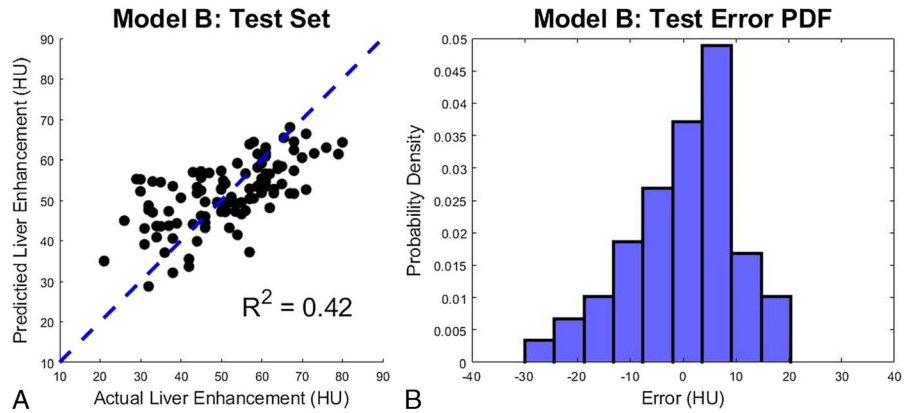

FIGURE 2. A, Scatter plot of the predictions vs actual HU values of test set for Model B (excludes monitoring data). The red line shows the perfect prediction, 1:1 line. B, Error partial distribution function (predictions–actual) of the prediction. Figure 2 can be viewed online in color at www.jcat.org.

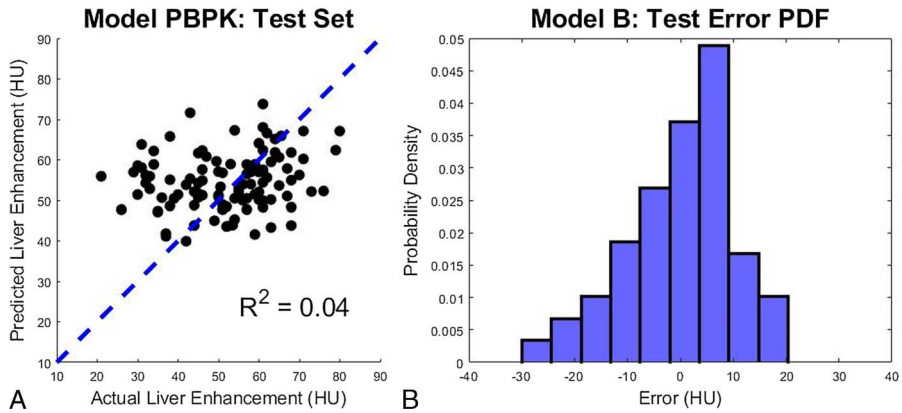

FIGURE 3. A, Scatter plot of the predictions vs actual HU values of test set for the PBPK model. The red line shows the perfect prediction, 1:1 line. B, Error partial distribution function (predictions–actual) of the prediction. Figure 3 can be viewed online in color at www.jcat.org.

patients to potential clinical and safety risks, such as contrast-induced nephrotoxicity or unnecessary additional dose from repeated scans for underenhanced patients.[2,21,22] Previous studies have shown the potential benefit of individualizing contrast administration protocols. Most prior work, however, have not taken advantage of the time dependence of contrast enhancement or focused on liver.[5–14] For this reason, in this article, we utilized the correlation information between different patient attributes and liver contrast enhancement and built contrast enhancement prediction models based on time-dependent patient data. In addition, we further demonstrated the utility of a prediction model to improve the consistency of contrast enhancement, as demonstrated in Figure 4.

Our results in Table 3 suggest that weight serves as the strongest predictor for and is inversely correlated with contrast enhancement in the liver parenchyma; greater weight implies lower enhancement. This observation is supported by previous studies which suggests similar conclusion regarding weight features.[10–14] Despite this concurrence, it is important to note that our data do not show stronger correlations between weight derivative features (calculated BMI and LBM) or age and contrast enhancement, unlike other studies have shown previously.[9,10] We note, however, that weight is not the only correlative factor, and thus a machine-learning based approach, as applied here, can provide improved prediction, and thus potential for optimization of contrast enhancement.

Unlike the PBPK model,[14–16] our models rely and were trained solely on clinical data to make predictions. Although the result of the PBPK model has been shown to agree with average clinical data, our prediction models showed higher predictive accuracy, as shown in Table 4. In addition, utilizing bolus tracking contrast monitoring data improves the prediction. This observation was expected as including such data can inform the model about the early dynamics of contrast perfusion in each patient's liver. Clinically, this supports the significance of acquiring bolus-tracking monitoring data before the diagnostic scan. Although having such model can help guide the administrator in determining the optimal time to conduct the diagnostic scan, relying on only monitoring data limits the possibility of having a truly personalized contrast administration protocol for each patient (eg, impossible to adjust bolus volume, injection rate, contrast media concentration). Both

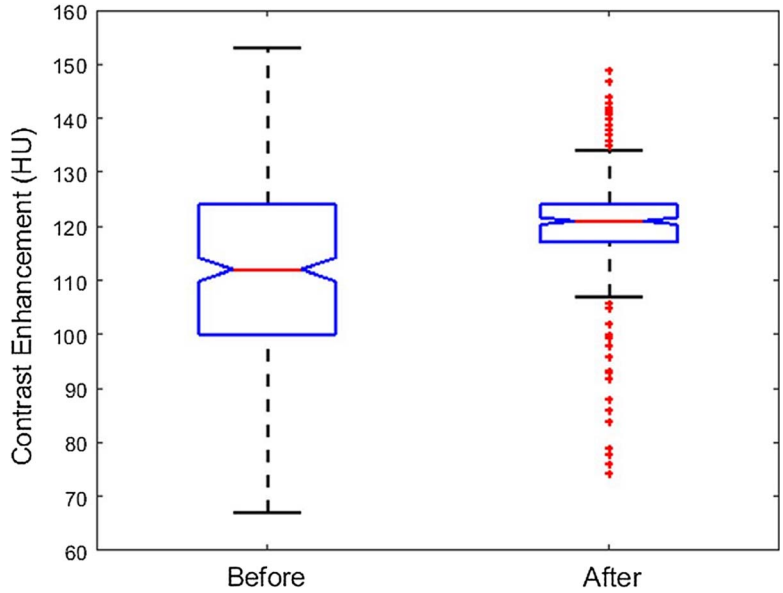

FIGURE 4. Box plots showing the effect of applying the hybrid predictive method to adjust the concentration of contrast media injected ($P < 0.001$). Figure 4 can be viewed online in color at www.jcat.org.

TABLE 4. Summary of the Goodness-of-Fit of the Prediction Models

	Model A	Model B	PBPK
Test R^2	0.75	0.42	0.04
Train R^2	0.96	0.61	N/A
MAE	4.45	7.89	10.86
RMSE	5.78	9.83	13.75

should ideally be taken into consideration when administrating the contrast imaging.

This study had several limitations. Although the images used in this study were diverse in terms of sex, height, weight, and other patient attributes and habitus, they were from the same institution. Future studies will include clinical data set from different clinical protocols and institutions to create a robust institution-agnostic model. Second, although we have demonstrated that weight is an important feature to predict contrast enhancement, there are other factors, such as heart rate, hydration level, and other cardiac function indicators, which were not considered due to unavailability of data. Furthermore, we mostly included patients with no known liver problems. Liver abnormalities (eg, hepatic cirrhosis) may influence contrast perfusion both in livers and other organs of interest, making it challenging to truly predict the dynamics of contrast enhancement. The described model can be extended to include vital signs and other patient specific features, if available. Lastly, although our model predicts enhancement of liver parenchyma at a certain time point, its predictive capability is constrained within a short time window, approximately from 60 to 75 seconds after the injection starts—due to the unavailability of data outside this clinically-acquired time window, preventing us from modeling a complete contrast enhancement curve. To solve this shortcoming, future studies may include perfusion imaging data to provide additional data points to train the model, especially during early arterial and delayed phases. Another alternate may be combining existing mathematical model to help inform the missing sections of the enhancement curve of an organ.

CONCLUSIONS

Patient attributes can be used to predict contrast enhancement over time. The performance of the prediction model can be further improved when bolus tracking contrast monitoring data are included. The prediction model can be used to define contrast enhancement administrations that target optimization, contrast media reduction, or consistency of enhancement across patients.

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