Patient-specific Prediction model of portal pressure reduction after Transjugular Intrahepatic Portosystemic Shunt (TIPS) Using CT-Derived anatomical parameters

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Abstract

Portale hypertensie, veelal het gevolg van levercirrose, wordt veroorzaakt door een verhoogde intrahepatische vaatweerstand en leidt tot een verhoogde drukgradiënt tussen de Vena Porta en de Vena Hepatica. Deze verhoogde drukgradiënt veroorzaakt boven een grens van 10 mmHg complicaties zoals refractaire ascites en varicesbloedingen. Wanneer medicamenteuze therapie niet voldoende is, is de plaatsing van een Transjugulaire Intrahepatische Portosystemische Shunt (TIPS) de standaard-behandeling. Deze procedure is een effectieve behandeling, maar brengt ook significante risico's met zich mee, waaronder een verhoogde kans op hepatische encefalopathie. Huidige computermodellen die de drukverandering na een TIPS plaatsing voorspellen, berekenen computationeel de flow binnen de patiëntspecifieke geometrie van het portale vaatbed. Dit kost enkele uren om te berekenen per patient en is daardoor niet klinisch toegankelijk. In de literatuur worden veelal correlaties beschreven tussen orgaangroottes en portale druk. Dit kan mogelijkheden bieden voor een klinisch toegankelijk computermodel dat als hulpmiddel gebruikt kan worden bij de pre-procedurale screening. Het doel van deze studie is het ontwikkelen van een op anatomie gebaseerd klinisch toepasbaar predictiemodel dat de portale drukgradiënt na een TIPS-plaatsing voorspelt op basis van CT-scans voor de TIPS plaatsing en enkele klinische parameters.

Methode: In deze retrospectieve modelontwikkelingsstudie werd een historisch patiëntencohort uit het Erasmus MC geanalyseerd. Patiënten uit het cohort werden geïncludeerd indien er een CT-scan beschikbaar was die binnen drie maanden voorafgaand aan de TIPS-procedure was gemaakt, en indien er drukmetingen beschikbaar waren van voor en na de TIPS-procedure. Lever- en miltvolumes werden automatisch gesegmenteerd met de TotalSegmentator module in 3D Slicer en vaatdiameters zijn handmatig gemeten volgens een gestandaardiseerd protocol. Er zijn twee aparte machine learning modellen ontwikkeld om de post tips Portal Pressure Gradient (PPG) te voorspellen: Een interpreteerbaar lineair regressiemodel en een complex tree-based XGBoost-model. De prestaties zijn geoptimaliseerd en gevalideerd met een 5x5 nested cross-validatieloop en geëvalueerd met de Mean Absolute Error (MAE), Root Mean Squared Error (RMSE) en de determinatiecoëfficiënt (R^2), en vergeleken met een baseline dummy regressor.

Resultaten: Uit het initiële cohort van 453 patiënten zijn uiteindelijk 144 patiënten geïncludeerd in het onderzoek. Het lineaire regressiemodel behaalde de beste voorspellende prestaties met een gemiddelde nested MAE van 2.00 $\pm$ 0.29 mmHg, een RMSE van 2.72 $\pm$ 0.45 mmHg en een R^2 van 0.13 $\pm$ 0.14. Het XGBoost-model presteerde minder goed met een gemiddelde nested MAE van 2.12 $\pm$ 0.26 mmHg, een RMSE van 2.90 $\pm$ 0.45 mmHg en een R^2 van 0.01 $\pm$ 0.12, wat vergelijkbaar is met de baseline van de dummy regressor (MAE: 2.14 mmHg). De definitieve formule van het lineaire regressiemodel gebruikt na regularisatie de variabelen pre-TIPS PPG, levervolume, de diameters van de vena porta, vena lienalis en vena mesenterica superior, de aanwezigheid van slokdarmvarices en de lever/BMI ratio.

Conclusie: Hoewel het lineaire regressiemodel op de vooraf vastgestelde drempelwaarde van een MAE van $\leq$ 2 mmHG scoort, tonen beide modellen een lage verklaarde variantie en een MAE die in de buurt ligt van de baseline dummy regressor. Dit kan erop wijzen dat alleen statische anatomische parameters binnen dit cohort onvoldoende voorspellend zijn om de drukrespons na TIPS accuraat te kunnen voorspellen. Dit kan mogelijk verklaard worden omdat factoren die niet meetbaar zijn op CT, zoals intrahepatische weerstand, collaterale circulatie en vaatcompliantie een belangrijke rol spelen in de portale drukverandering. Het ontwikkelde model is niet accuraat genoeg voor zelfstandige klinische besluitvorming, maar kan wel een waardevolle fundering leggen voor toekomstig onderzoek waar het model wordt uitgebreid met grotere multicenter cohorten of het vergelijken van TIPS met alternatieve interventies zoals miltembolisatie.

Take-home message: Statische anatomische parameters zijn met de methodes beschreven in dit verslag niet voldoende voor het accuraat voorspellen van de portale drukgradiënt na een TIPS-plaatsing.

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2 Introduction

Portal hypertension is caused by increased hepatic vascular resistance, most commonly due to liver cirrhosis. In portal hypertension, there is an increased Hepatic Venous Pressure Gradient (HVPG >5 mmHg), which can lead to severe complications such as refractory ascites, hepatorenal syndrome and variceal bleeding when exceeding 10 mmHg. [1]

Figure 1: Stages of portal hypertension

When pharmacological treatment fails, the standard procedure is the placement of a 'Transjugular Intrahepatic Portosystemic Shunt' (TIPS). During this procedure, a bypass is created percutaneously within the liver to divert part of the blood flow directly from the portal vein to the hepatic vein.

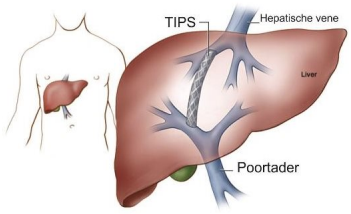

Figure 2: Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Although TIPS treatment is effective, the procedure is associated with significant risks, such as procedural burden and an increased risk of hepatic encephalopathy, which is accompanied by confusion, drowsiness, and concentration problems [2].

There is also increasing interest in alternative treatment options, such as (partial) splenic embolisation, in which blood supply to the spleen is reduced in order to decrease portal inflow and thereby lower portal pressure. Although potentially less invasive, limited evidence exists regarding its pressure reduction and effectiveness compared with TIPS.

Furthermore in elective cases, clinicians must continuously balance the expected therapeutic benefit of portal pressure reduction against the risk of excessive shunting and subsequent hepatic encephalopathy. Currently, this decision is primarily based on clinical experience and patient characteristics, while the individual hemodynamic response to TIPS remains difficult to predict before the procedure. As a result, uncertainty remains regarding both the expected effectiveness of TIPS and the optimal stent diameter.

To balance the expected pressure reduction against the risk of potential complications, the development of a model capable of predicting the hemodynamic response prior to intervention would provide valuable support in clinical decision-making.

Existing models for predicting hemodynamic changes rely on computationally modelling the dynamic flow using the patient specific portal geometry. A major limitation of these flow-based models is that the required computations are very time-consuming requiring several hours per patient, and some required measurements are often not routinely available in clinical practice [3]. Portal pressure is determined not only by intrahepatic vascular resistance but also by blood inflow from the spleen and the geometry of the portal venous system. These hemodynamic characteristics are reflected anatomically by organ size and the dimensions of the portal vasculature. Previous studies [4] have demonstrated that liver volume (associated with intrahepatic resistance) and spleen volume (associated with portal inflow) are strongly correlated with portal hemodynamics and changes in portal pressure. By incorporating these patient-specific anatomical parameters, the hemodynamic response may therefore be estimated more accurately.

The present study aims to develop an anatomy-based prediction model for estimating the reduction in portal pressure following TIPS placement. Such a model could assist clinicians in making patient-specific treatment decisions by providing a pre-procedural estimate of the expected pressure reduction based solely on CT imaging.

In contrast to these existing approaches, the present study focuses exclusively on routinely available CT-derived anatomical parameters. By avoiding complex flow measurements and advanced imaging techniques, the proposed model aims to provide an interpretable and clinically accessible tool that can be applied in routine pre-procedural assessment.

In the future, this model may also be used to compare the expected hemodynamic effects of TIPS with alternative treatment options, such as splenic embolisation, thereby supporting a more evidence-based selection between different therapeutic strategies.

Ultimately, this research may contribute to a more personalized treatment approach for patients with portal hypertension.

We hypothesize that a combination of CT-derived anatomical parameters can be used to predict portal pressure reduction after TIPS placement. Because portal hemodynamics are governed by complex interactions between vascular anatomy and physiological processes, we expected that a non-linear machine learning algorithm such as XGBoost would outperform a linear regression model by better capturing these relationships. Although the predictive performance may be lower than that of more complex flow-based computational models, the use of routinely available anatomical parameters may provide sufficient accuracy for clinically relevant estimation while substantially improving practical applicability and interpretability.

3 Materials and Methods

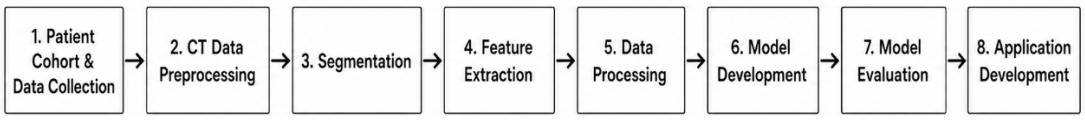

Figure 3: Work Flow of the method

In figure 3 the work flow of the method is visualised in a flowchart. Starting with data collection in order to eventually end with developing an app around the develepod prediction model.

3.1 Study design

This study is a retrospective model development study based on an existing cohort of patients who underwent a Transjugular Intrahepatic Portosystemic Shunt (TIPS) procedure at Erasmus MC. Clinical data and pre-procedural CT scans were retrospectively collected to develop and validate a patient-specific prediction model for predicting the Portal Pressure Gradient (PPG) after TIPS.

3.2 Patient cohort

An existing cohort of patients who underwent TIPS placement at Erasmus MC between 2007 and 2023 was provided by the supervising clinicians. Each patient record was manually reviewed to determine whether a contrast-enhanced CT scan had been performed within three months prior to the TIPS procedure. This time interval was chosen to minimize potential anatomical and hemodynamic changes between image acquisition and the TIPS procedure while maintaining a sufficiently large study cohort. This interval is in line with current clinical practice, where cross-sectional imaging obtained within the previous three months is considered adequate for TIPS planning according to the EASL Clinical Practice Guidelines [5], the following sources of cites support this time frame [6]. Longer inclusion windows of six and twelve months were considered during study design. However, including these would only result in a limited increase in the number of eligible patients while introducing a greater risk of anatomical and clinical

changes occurring between imaging and TIPS placement. Therefore, the potential gain in sample size was considered insufficient to justify the reduction in temporal validity.

Only patients with an available CT scan within this time window and sufficient image quality for anatomical analysis were included. Patients with incomplete imaging or major anatomical abnormalities that could interfere with segmentation, such as previous hepatectomy or other relevant surgery, were excluded from further analysis.

3.3 Parameter selection

The anatomical and clinical parameters included in the prediction model were selected based on a preceding systematic review conducted as part of this research project. The review investigated which parameters obtainable from routine CT imaging or patient medical records have been reported to be associated with portal pressure or portal hemodynamics. Because the machine learning models have possibilities for strong regularisation and feature selection, all parameters that were identified as having a statistically significant association with portal pressure in at least one included study were considered eligible for inclusion in the initial model development. All parameters were included to minimize the risk of omitting potentially relevant predictors. This approach was chosen to ensure that the model was based on the current available evidence while remaining clinically applicable using routinely available pre-procedural data.

3.4 Data collection

For each included patient, their medical record was identified in the electronic patient chart using the provided TIPS cohort list. The corresponding CT examination was exported in anonymized DICOM format and stored under a unique study cohort number on two secure encrypted hard drives. The corresponding electronic medical records were manually reviewed to collect relevant clinical variables, including body mass index (BMI), the presence of ascites, oesophageal varices and liver cirrhosis. Furthermore, the CT scans were visually inspected to verify that the entire upper abdomen was included and that all anatomical structures required for segmentation were completely visible.

Because this was a retrospective cohort, not all CT examinations contained standardized arterial and portal venous phases. To avoid excessive loss of patients, scans acquired in other contrast phases were also included provided that the relevant anatomical structures could be visualised adequately for reliable measurement.

From the hard drive, the CT scan was imported to 3D slicer to extract the volumes and diameters of the relevant parameters. All extracted anatomical measurements and clinical variables were recorded in a standardized data collection sheet on the encrypted hard drive using the assigned study cohort number.

3.5 Measurement protocol

All anatomical measurements were performed according to a predefined standardized measurement protocol.

Liver and spleen volumes were obtained by applying the TotalSegmentator module in 3D slicer for automatic organ segmentation. The generated segmentations were visually inspected and, where necessary, corrected before the final organ volumes were extracted.

For each vessel, a fixed anatomical landmark was defined prior to the start of the measurements to ensure consistency between patients and observers. This protocol can be found in Appendix B.

The vessel diameter was measured perpendicular to the vessel axis from inner wall to inner wall at the predefined anatomical location. If the vessel was not clearly visible at this exact location due to image quality, tortuosity, branching or anatomical variation, the nearest location where the vessel remained clearly visible over the longest continuous segment was selected. Measurements were performed on the slice with widest visible cross-section while remaining as close as possible to the predefined anatomical landmark.

This standardized approach was used to minimize measurement variability while maintaining anatomical consistency across all patients.

To reduce intraobserver variability, each vascular diameter measurement was performed three consecutive times by the same observer. The final recorded diameter was calculated as the average of these three measurements.

To assess interobserver reproducibility, a random subset of 18 CT scans was independently re-measured by a second observer following the same measurement protocol. Agreement between observers was quantified using the Intraclass Correlation Coefficient (ICC).

3.6 Law and regulation

This study was conducted using retrospective patient data obtained from Erasmus MC. The patient cohort was conducted in accordance with the guidelines of the Declaration of Helsinki and Istanbul and the principles of Good Clinical Practice. The study protocol of the cohort was reviewed and approved by the Medical Ethics Review Committee (METC) of the Erasmus Medical Center in Rotterdam, the Netherlands (approval number MEC-2021-0594).

All researchers involved in this project were affiliated with Erasmus MC through a hospitality agreement, allowing access to the required clinical data and imaging within the institutional regulations.

Patient records were accessed within the secure Erasmus MC environment to collect the required clinical variables and imaging data. After inclusion, all exported CT scans were downloaded anonymously and associated research data were pseudonymized by assigning each patient a unique study cohort number. Directly identifiable personal information was not included in the exported dataset. All anatomical measurements, clinical variables, and subsequent analyses were recorded exclusively under this cohort number, ensuring that the research dataset did not contain directly identifiable patient information.

The pseudonymized research data and CT images were stored on encrypted password-protected external hard drives dedicated to this project. Access to these data was restricted to the research team and supervising clinicians. The storage devices were kept in a secure location and were not connected to publicly accessible cloud services.

Following completion of the project, all locally stored research data will be deleted.

3.7 Model development

To predict the post-TIPS Portal Pressure Gradient (PPG) based on anatomical CT parameters, pre-TIPS PPG and some clinical variables, a machine learning model was developed. The results of our systematic review about anatomical parameters were inconclusive as to whether anatomical variables correlate linearly or non-linearly with portal pressure changes (Appendix E). Therefore, two separate machine learning models were developed: An interpretable linear regression model and a complex tree-based eXtreme Gradient Boosting (XGBoost) model. One final model will be chosen and implemented in an application, based on validity and ease of use.

3.7.1 Data preprocessing and feature engineering

Prior to model training, the patient dataset underwent a standardized preprocessing pipeline.

- Feature engineering: In our systematic review (Appendix E), several volume or diameter ratio's showed a significant correlation with portal pressure. The following features were implemented in our dataset:
  - spleen volume (cm^3)/$livervolume(cm^3)$
  - spleen volume (cm^3)/BMI
  - liver volume (cm^3)/BMI
  - superior mesenteric vein (mm) / splenic vein (mm)
  - portal vein (mm) / splenic vein (mm)

  These engineered ratio features were included only in the linear regression model. The XGBoost model can learn complex interactions between individual variables through sequential decision tree

splits. Therefore, explicitly adding ratio features was considered unnecessary and could introduce redundant information, increasing the risk of overfitting in a relatively small dataset.
In contrast, linear regression cannot inherently model interactions or ratio-based relationships between variables, making explicit feature engineering potentially beneficial for predictive performance. For the linear regression model, the introduced multicollinearity was mitigated through Elastic Net regularisation, where the L2 (Ridge) penalty stabilizes the estimated coefficients in the presence of correlated predictors.
In the development of the prognostic models, the decision was made to not include the stent diameter. Due to the clinical workflow of a TIPS procedure, the definitive stent diameter is dynamically determined during or immediately after the intervention, adjusted step-by-step based on how the portal pressure reacts to the shunt placement. Because the final stent diameter is individualized and determined iteratively based on the patient's hemodynamic response during the procedure, the dataset contains only a single clinically optimized diameter for each patient. Consequently, the available data do not provide sufficient variation in stent diameters within the same physiological context to reliably model or quantify the independent effect of all stent diameter sizes on post-TIPS portal pressure.
Because the final stent diameter is based on the patient's intraprocedural hemodynamic response to TIPS, it is not available during the pre-procedural assessment. Including stent diameter as a predictor would therefore introduce data leakage, as the variable is partly determined using information closely related to the outcome itself. Excluding stent diameter ensures that both the Elastic Net and XGBoost models function strictly as pre-interventional prognostic tools based solely on information available before TIPS placement.

- Missing data: Missing values occurred when clinical variables could not be retrieved from the electronic patient record or when anatomical parameters could not be reliably measured on the CT scan. Anatomical measurements were marked as missing when the structure was not sufficiently visible due to image quality, absence of the required contrast phase in combination with low image quality, anatomical variation or when the predefined measurement location could not be identified with sufficient confidence. For clinical variables, BMI was recorded as missing when it was unavailable in the patient record. When the presence of ascites, oesophageal varices and cirrhosis were not documented, they were assumed to be absent and recorded as such. To prevent the loss of complete patient cases due to listwise deletion, missing values were handled using model-specific strategies aimed at maximizing predictive performance.
  For the linear model, the Scikit-learn implementation requires complete datasets and cannot process missing values (NaN). Therefore, K-Nearest Neighbors (K-NN) imputation was applied to the dataset exclusively for this model. The K-NN imputer estimates missing measurements based on the characteristics of the k most similar patients in the dataset.
  XGBoost and other tree-based models feature a built-in mechanism for handling missing data known as sparsity-aware split finding. During the training process, the algorithm learns the optimal direction in the tree for instances with missing values. Because imputation can introduce unwanted noise, the XGBoost model was trained and evaluated on the original, non-imputed dataset.
- Normalization: all continuous variables were standardized using Z-score normalization (StandardScaler). This scales all variables to a uniform range. This prevents features with larger numerical values (such as spleen volume) from disproportionately affecting the loss function and model regularisation. This scaling was only done for the linear regression model, since the XGBoost model is based on decision trees and makes splits based on the relative rank order of individual features, making its architecture insensitive to the scale or magnitude of the input variables.

3.7.2 Model architectures and feature selection

Linear regression model

Linear regression estimates a linear 'best-fit' line by minimizing the distance between the line and all the training data points. Each variable is assigned a specific weight. To generate a prediction, the model multiplies each clinical measurement by its weight and sums them together, and adds a constant known

as the intercept.

The model uses ElasticNet regularisation. This is a combination of L1 (Lasso) and L2 (Ridge) regularisation. L1-regularisation pushes the coefficients of irrelevant features to exactly 0, acting as a strict feature selector. The features were decided as irrelevant when it had an absolute value below 0.0001. The L2-regularisation ensures mathematical stability when the input variables show strong correlations, such as spleen volume, and spleen volume/BMI. The balance between these two penalties is tuned during hyperparameter tuning.

This formula can easily be interpreted by a clinician and is very explainable. However, this model can only estimate linear relationships. When the portal pressure changes in a non-linear way, this model fails to accurately describe it. Furthermore, this model is not suited for working with missing data points. If some variable is not available in the clinic, it cannot accurately predict the portal pressure after TIPS. A way to work around this flaw is to store all training data in the final application and calculate missing data points using K-NN imputation. Storing patient data is neither ethical nor safe; therefore, we will refrain from implementing this into the application.

XGBoost relies on a collection of discrete, hierarchical structures called Regression Decision Trees. A single regression tree operates like a flowchart. It takes the patient population and splits it into subgroups based on sequential binary questions. Patients follow the path based on their clinical and anatomical metrics, until they end up in a final 'leaf node'. This leaf node assigns them a predicted PPG value based on the average of all PPG values of the patients within that leaf node.

XGBoost uses an ensemble optimization strategy known as gradient boosting. Instead of constructing one super complex decision tree, the algorithm iteratively builds a sequence of small, shallow trees. The initial tree generates a baseline prediction. The next tree is trained to predict the residuals (errors) made by the previous tree. This process is repeated hundreds of times, with each tree trying to correct the remaining errors of the collective of previous trees. The final prediction for a given patient is the regularized, weighted sum of the outputs across the entire sequence of trees.

This approach has the potential to model very complex relationships between different variables, but it can also easily overfit to the training data. Strict hyperparameter tuning is necessary to avoid overfitting.

To interpret the internal decision making of all the combined decision trees, feature importance scores were calculated by averaging the percentage of split contributions across all five folds.

3.7.3 hyperparameter tuning

Hyperparameters refer to the structural configurations and algorithmic settings of a model. They control how the model learns, regulate its complexity and manages the trade-off between accurately fitting the training cohort and maintaining the ability to generalize to unseen patients. To avoid the inefficiencies of hyperparameter tuning with a GridSearch, this study used Optuna, an automated hyperparameter optimization framework. Optuna employs a Bayesian optimization algorithm known as the Tree-structured Parzen Estimator (TPE). It treats the optimization process as an adaptive search using gradient descent to find the optimal set of hyperparameters. When log=True is used, Optuna searches on the logarithmic scale, which makes it search more intensely through the smaller values. In this study we used 200 trials for Optuna to find the best set of hyperparameters. Hyperparameter tuning was only performed in the inner loop of the nested cross validation, preventing any data leakage to the test set.

The following hyperparameters were optimized for the linear regression model:

- Alpha (range: 0.001 - 1): this is the regularisation parameter and controls the penalty applied to the model's coefficients. A higher alpha shrinks the coefficients more and prevents the model from over-relying on individual variables
- L1_ratio (range: 0 - 1): This number controls the ratio between Lasso (L1) and Ridge (L2) regularisation, where 0 is pure L2, and 1 is pure L1.
- n_neighbours (range: 2 - 15): This parameter determines the amount of neighbours in the K-NN imputation mechanism. Selecting the right amount of neighbours balances between the oversensitivity of individual outliers and overgeneralizing by averaging across an overly large segment of the dataset.

The following hyperparameters were optimized for the XGBoost model:

- Learning rate (range: 0.001 - 0.05, log=True): This parameter scales the contribution of each newly added tree.
- Maximum tree depth (range: 1 - 5): This limits the amount of splits allowed within a single tree.
- Minimum child (range 1 - 30): This parameter determines the minimal number of patients that must be within a terminal node.
- Gamma (range: 0-10): This parameter specifies the minimum loss reduction required to make a split. This ensures that only a split is made when it is statistically advantageous.
- Subsample and Colsample (range 0.5-0.9): These introduce controlled stochasticity into the training process. subsample specifies the fraction of the patient cohort randomly sampled for each tree, while colsample dictates the fraction of clinical features available at each split. These parameters prevent the model from over-relying on a single dominant variable.
- Alpha & lambda (Range 0.001 - 10, log=True): These parameters represent L1 and L2 regularisation.

3.8 Validation

To validate the model performance and tune the hyperparameters of the model, 5x5 nested cross-validation is used. The data set is split into an inner and an outer cross validation loop to guarantee the independence of the testing data from trainings data, and prevent any data leakage.

The nested validation structure is split into two seperate loops:

- **Inner Loop:** This loop is used exclusively for feature selection and optimizing the hyperparameters of the algorithms via the Optuna framework. Within this loop, specific configuration settings are fine-tuned, such as the degree of feature selection (λ) and ratio's for the linear regression model, as well as the parameters regulating decision tree complexity for the XGBoost model.
- **Outer loop:** The outer loop is solely used to independently validate the performance of the optimized model configuration delivered by the inner loop. As this data is not used for training the model, it provides the best estimation of the models performance on unseen patients.

To quantitatively assess and compare the accuracy of both the linear regression model and the non-linear XGBoost model, the model outputs are compared against the actually measured pressure changes using three primary metrics:

- **Mean Absolute Error (MAE):** This represents the average absolute difference between the predicted post-TIPS portal pressure and the actual measured portal pressure. The MAE is the most clinically relevant metric for the attending physician, as it directly reflects the average prediction error in mmHg.
- **Root Mean Squared Error (RMSE):** This metric (Formula A) squares the errors before calculating the average, thereby penalizing larger prediction errors more heavily. This provides an indication of the presence of larger outliers in the model predictions.
- **Coefficient of Determination (R^2):** The R^2 value establishes the overall explanatory power of the model. This value serves as a measure of the proportion of the total variance in the post-TIPS pressure that can be explained by the CT-derived anatomical input variables in the model.

To evaluate the predictive utility of the developed models, their performance was tested against a baseline dummy regressor. This baseline model simply predicts the cohort's mean post-tips PPG for every patient, establishing a minimum statistical threshold. For the developed models to demonstrate any clinical value, they must significantly outperform this naive baseline, proving that they have successfully captured meaningful, non-random physiological patterns within the anatomical data.

After a thorough evaluation of the model's performance, and thereby the used training methodology, a new model is trained on the entire cohort to maximize statistical power. This new model is implemented in the application. Interobserver reliability was quantified using the Intraclass Correlation

Coefficient (ICC). Specifically, a two-way random-effects model based on single measures and absolute agreement—conventionally denoted as $ICC_{2,1}$—was applied to the multi-observer measurements of each of the six individual vessel segments [7].

Clinical performance benchmarks

The maximum allowable threshold for the Mean Absolute Error (MAE) is set at $\leq$ 2 mmHg. This boundary is reasoned by the narrow margins within the clinical management of portal hypertension, in combination with a realistic view on the accuracy an anatomical based prediction-model is able to reach. Clinically Significant Portal Hypertension (CSPH) is defined by an HVPG of $\geq$ 10 mmHg, while a critical threshold for variceal bleeding and the universal post-interventional target is anchored around 12 mmHg. As the transition between a stable clinical profile and an acute, life-threatening risk category spans a window of merely 2 mmHg, a mean error exceeding this boundary could lead to misclassifications of a patient's hemodynamic risk. [1]

3.9 Application development

The goal of our model is to help make a decision about the type of treatment they want to deliver, based on an estimate of the possible portal pressure after a TIPS procedure. In order to make the model more accessible to medical teams, we wanted to simplify the use of the model by wrapping it into a clear frontend design.

Instead of using Python to present the model output, we extracted the resultant equation of our model output and present both the input and output on the same screen. The intended user of our application is the multidisciplinary medical team working on a Transjugular Intrahepatic Portosystemic Shunt procedure, in order to make a quick patient specific prediction before placing a portosystemic shunt. The anatomical parameters first have to be obtained from the CT scans through segmentation and manual measurement. using total segmentation and 3D slicer.

The application itself, in combination with our model output, is only a decision support tool. It is not meant as an independent decision maker. The final interpretation and decision on the chosen procedure still falls on the surgeon. We only present the expected pressure after each procedure.

The functional code of the application can be divided into three main parts, which are included in the appendix. First, the file fields.ds defines which values the user has to enter into the application. These include the raw input values, such as pressure gradient, BMI, CT volumes, vessel diameters and clinical signs, as well as the ratios that are calculated from these values. Second, the file predict.ts contains the linear model that was implemented in the application. This model uses the entered values and the extracted coefficients to calculate the expected portal pressure. The same file also gives the contribution of the different variables and places the predicted value into a clinical category. Third, the file xgb.ts contains the XGBoost model. This file reads the exported XGBoost model structure and uses the same input values as the linear model to calculate a prediction. Because both models use the same input definitions and return the same type of output, the application can present the results of both models in the same screen structure.

3.10 Software

CT image segmentation and anatomical measurements were performed using 3D Slicer (version 5.10.0, Kitware Inc., USA) with the TotalSegmentator extension (version 2.13.0) with nnU-Net (version 2.8.0), running on CUDA / NVIDIA RTX 1000 Ada (6 GB). Data preprocessing, model development and statistical analyses were performed in Python (version 3.13.7) using the Scikit-learn (version 1.8.0) and XGBoost (version 3.2.0) libraries. Hyperparameter optimization was performed using Optuna (version 4.8.0). The final model outputs were implemented in the application prototype, which was developed in TypeScript.

4 Results

4.1 Inclusion

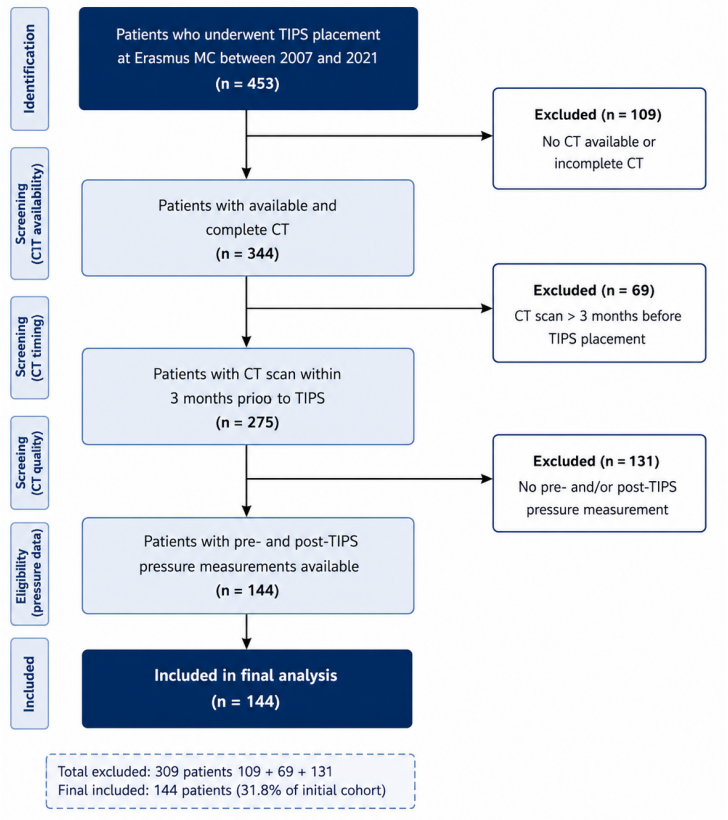

Figure 4: Flowchart of patient selection and exclusion for the TIPS cohort

The patient selection process, including specific reasons for exclusion, is systematically outlined in the patient flow diagram (Figure 4). Initially, a total of 453 patients who underwent a Transjugular Intrahepatic Portosystemic Shunt (TIPS) procedure at Erasmus MC were identified from the institutional database.

Following the predefined inclusion and exclusion criteria, significant cohort attrition occurred. The primary drivers for patient exclusion were incomplete clinical data records and the absence of pre- or post-procedural portal pressure gradient (PPG) measurements. Furthermore, patients were omitted if the temporal window between the baseline CT acquisition and the subsequent TIPS intervention exceeded the maximum threshold of three months. Also a substantial subset of patients was excluded due to imaging constraints, which included completely missing computed tomography (CT) datasets, unreadable scans or CT-images without full organ displayed precluded reliable automated or manual segmentation. Consequently, a final cohort of $n = 144$ patients met all criteria and was included for subsequent parameter extraction and predictive modeling.

4.2 Cohort Statistics and Anatomical Metrics

The baseline clinical characteristics, post-hoc volumetric segmentations, and vascular diameter measurements of the final study cohort are detailed in appendix K.

The automated and organ volumetry resulted in a mean spleen volume of 693.8 ± 395.0 ml, which markedly deviates from standard physiological reference ranges. This extensive tissue expansion is further reflected in a highly elevated mean spleen-to-liver volume ratio of 0.37 ± 0.21. Hemodynamically, the severity of portal hypertension and the technical success of the subsequent intervention are clearly demonstrated by the portal pressure gradients; the mean pre-procedural PPG was severely elevated at

16.1 ± 5.3 mmHg, which was reduced significantly to a mean post-procedural PPG of 5.7 ± 2.9 mmHg following TIPS placement.

Regarding data , the overall availability of the extracted features remained robust across the majority of parameters. Full data completeness (100.0%) was achieved for volumetric indices (liver and spleen volumes) and baseline clinical designations. The lowest data availability was observed for BMI and its derived indices (Liver/BMI and Spleen/BMI) at 84.0%, as well as the splenic artery diameter at 89.6%.

4.3 Interobserver reproducibility

Interobserver agreement was assessed in 18 randomly selected CT scans. The ICC values ranged from 0,26 to 0,80 for the different vessel diameter measurements, indicating good to excellent agreement between observers.

4.4 Linear model

The nested cross validation yielded the following prediction accuracy scores on unseen testing data for the linear regression model:

- Average Nested MAE: 2.00 mmHg (± 0.29)
- Average Nested RMSE: 2.72 mmHg (± 0.45)
- Average Nested R^2: 0.13 (± 0.14)

The R^2 score of 0.13 indicates that approximately 13% of the total variance in post-TIPS portal pressure can be explained by the anatomical and clinical parameters included in the model.

The Optuna framework found the following hyperparameters for the final model trained on 100% of the trainingsdata. Best hyperparameters of final model trained on 100% of the cohort: Alpha: 0.4629 L1 Ratio: 0.4657 KNN Neighbors: 11

By mathematically scaling the weights back to their original scales, training the final model on the entire cohort resulted in formula 1. All parameters not listed in this equation were shrunk to zero by regularisation due to a lack of predictive value.

$$\begin{aligned} \mathrm{PPG}_{\mathrm{post}} = 1.2397 \\ &+ 0.0003 \times \text{Liver volume (mL)} \\ &+ 0.0118 \times \text{Portal vein diameter (mm)} \\ &+ 0.0039 \times \text{Splenic vein diameter (mm)} \\ &+ 0.0382 \times \text{Superior mesenteric vein diameter (mm)} \\ &- 0.1140 \times \text{Oesophageal varices} \\ &+ 0.0134 \times \text{Liver/BMI} \\ &+ 0.1529 \times \mathrm{PPG}_{\mathrm{pre}}. \end{aligned} \tag{1}$$

4.5 XGBoost model

The evaluation of the XGBoost model on unseen testing data resulted in the following metrics:

- Average MAE: 2.12 mmHg (± 0.26)
- Average RMSE: 2.90 mmHg (± 0.45)
- Average R^2: 0.0107 (± 0.1231)

Table 1 shows the average feature importance scores across all five cross-validation folds.

Table 1: Feature importance of the XGBoost model averaged over the five cross-validation folds.

[h] height**Feature**	**Importance**
PPG_combi_pre	0.150
Liver volume (mL)	0.119
Left renal vein diameter (mm)	0.113
Superior mesenteric vein diameter (mm)	0.098
Portal vein diameter (mm)	0.090
Splenic vein diameter (mm)	0.085
BMI	0.081
Spleen volume (mL)	0.079
Proper hepatic artery diameter (mm)	0.069
Splenic artery diameter (mm)	0.067
Esophageal varices	0.037
Refractory ascites	0.012

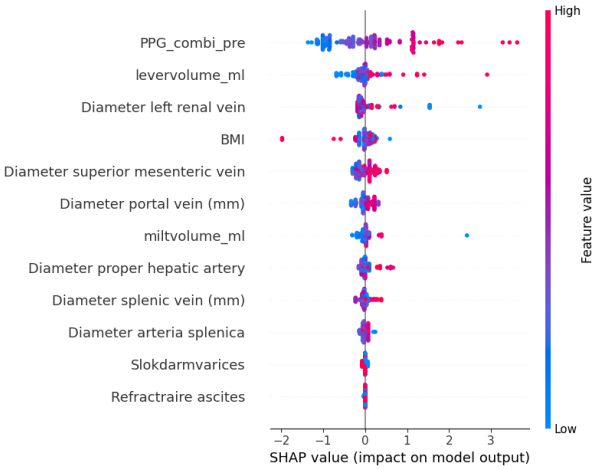

Figure 5: SHapley Additive exPlanations (SHAP) summary plot of the XGBoost model. This figure shows the direction of the change in predicted portal pressure based on the given variable. The parameters are sorted from top to bottom based on their predictive power. Points plotted to the right of the zero line mean that the parameter increased the predicted Portal Pressure Gradient (PPG) for that patient. Points to the left mean it decreased the predicted pressure. Red represents a high value for that variable, and blue represents a low value.

4.6 Model Comparison

To determine whether either prediction model learned any meaningful patterns from the training data, their performance was compared to a baseline dummy regressor that simply predicts the mean post-TIPS PPG. The statistics of all three models are summarized in table 2.

4.7 Application

The output of the application presents the predicted portal pressure after TIPS in a modal form form. This could later be changed to show two predictions, one for TIPS and one for splenic embolisation, to easily show the expected resultant pressures after both surgeries.

The linear regression equation has been presented such that it can easily be altered by the user if they wish to implement their own model. the same counts for the XGBoost model which can easily be imported into the app to function with the variables it has stored within its json file.

The complete user interface and layout of the application are presented in Appendix M.

Table 2: Performance Comparison of the Predictive Models Against the Baseline Dummy Regressor. The performance of the models is expressed in the Mean Absolute Error (MAE), Root Mean Squared Error (RSME) and the coefficient of determination (R^2).

Model Architecture	**MAE (mmHg)**	**RMSE (mmHg)**	R^2 **Score**
Dummy Regressor (Baseline)	2.14	2.92	0.000
Linear Regression	2.00 ± 0.29	2.72 ± 0.45	0.130 ± 0.140
XGBoost Regressor	2.12 ± 0.26	2.90 ± 0.45	0.0107 ± 0.1231

5 Discussion

5.1 Main findings

The present study aimed to develop a patient-specific prediction model for portal pressure reduction after TIPS placement using routinely available CT-derived anatomical variables and some clinical variables. Contrary to the initial expectation that a non-linear machine learning algorithm would outperform a linear model, the Elastic Net regression model achieved the best overall predictive performance, with a lower MAE (2.00 mmHg), lower RMSE (2.72 mmHg) and higher explained variance ($R^2 = 0.13$) than the XGBoost model. Although the Elastic Net model outperformed the XGBoost model, both models demonstrated limited predictive performance. The low explained variance ($R^2 = 0.13$ for the linear model and $R^2 = 0.01$ for XGBoost) indicates that CT-derived anatomical parameters explain only a limited proportion of the inter-patient variability in post-TIPS portal pressure, performing only marginally better than the dummy regressor. The XGBoost model performed only slightly better than the baseline dummy regressor, indicating poor generalization to unseen patients.

One possible explanation is that the available cohort of 144 patients was relatively small for training a highly flexible tree-based model. Complex machine learning algorithms generally require substantially larger datasets to reliably learn non-linear interactions without overfitting. In contrast, the Elastic Net model benefits from strong regularisation, which reduces model complexity and improves robustness in smaller datasets. Another explanation may be that the underlying relationship between anatomical parameters and portal pressure reduction is predominantly linear. In such situations, more complex machine learning algorithms may add unnecessary model complexity without improving predictive performance.

The final linear model included only a limited subset of the initially selected variables, including pre-TIPS portal pressure, liver volume, liver volume/BMI and the diameters of the portal vein, splenic vein and superior mesenteric vein, while many other candidate variables received coefficients close to zero through Elastic Net regularisation. This suggests that these excluded variables contributed little additional information once the remaining predictors were included.

From a physiological perspective, this finding is plausible. Portal pressure is primarily determined by the balance between portal venous inflow and intrahepatic vascular resistance. Liver volume may indirectly reflect the amount of functional hepatic parenchyma and intrahepatic vascular capacity [8], while the diameters of the portal vein, splenic vein, and superior mesenteric vein reflect the magnitude of splanchnic venous inflow and portal hypertension. Pre-TIPS portal pressure logically remained one of the strongest predictors, since patients with a higher baseline pressure generally have a larger pressure gradient available for decompression after shunt creation. The retention of these variables by the Elastic Net model is therefore physiologically plausible and consistent with the current understanding of portal hypertension.

Several engineered ratio features and anatomical variables were effectively excluded from the final Elastic Net model through regularisation. Most ratio variables contributed little additional information once the individual anatomical measurements were included. Since these engineered features were derived from the original parameters, they introduced substantial collinearity. Elastic Net regularisation is specifically designed to suppress redundant predictors, thereby retaining only variables that provide independent predictive information.

Interestingly, our preceding systematic review and meta-analysis demonstrated moderate correlations

between spleen volume ($r = 0.64$, $n = 7$), portal vein diameter ($r = 0.43$, $n = 5$), and splenic vein diameter ($r = 0.42$, $n = 4$) and baseline portal pressure (HVPG) (Appendix E). In the present study, portal and splenic vein diameters remained in the final model, whereas spleen volume and several ratio features were effectively removed. This mismatch in correlation between the literature and our patient cohort can possibly point towards a difference between predicting portal pressure in general and predicting a complex hemodynamic response to a mechanical bypass shunt.

The margins in portal hypertension are very narrow. The difference between a stable patient and one with life-threatening complications such as oesophageal varices is only 2 mmHg [1]. Our best model scores just on the set boundary of 2 mmHg. This indicates that the model is not accurate enough to be used in a clinical setting for decision making, although it might give a hint in the right direction.

Previous studies reporting non-invasive prediction of portal hypertension generally focused on predicting baseline portal pressure or clinically significant portal hypertension rather than the pressure change after TIPS placement. Moreover, many published models rely on computational fluid dynamics, Doppler-derived flow measurements, elastography or high-dimensional radiomic features, resulting in substantially higher predictive performance at the expense of clinical applicability. In contrast, the present study deliberately restricted the input variables to routinely available anatomical CT measurements, aiming to maximize simplicity, interpretability and ease of implementation in daily clinical practice. The lower predictive performance observed in this study therefore represents a trade-off between model accuracy and clinical feasibility.

Despite the modest predictive performance, this study has several important strengths. First, the model was developed using routinely acquired pre-procedural CT scans that are already part of standard clinical care, eliminating the need for additional imaging, flow measurements or invasive measurements. Second, the study focused on a patient specific prediction of post-TIPS portal pressure, which is directly relevant for pre-procedural clinical decision making. Third, all anatomical measurements were performed according to a standardized protocol, improving reproducibility. In addition, the use of 5x5 nested cross-validation and comparison with a baseline dummy regressor provided a robust internal evaluation of model performance. Finally, the use of an interpretable Elastic Net regression model allows clinicians to directly understand the contribution of individual anatomical parameters to the predicted portal pressure.

5.2 Limitations

As stated in the results, the total amount of available data was significantly limited by inclusion and quality criteria, resulting in a reduction of the final study cohort to n = 144 patients. The significant reduction in sample size affects the statistical power of both the linear and XGBoost prediction models, potentially limiting the models' generalizability and their capacity to map the relations between the parameters and the pressure change. The thoroughly reduced sample size also increases the risk of overfitting.

Furthermore some datapoints were missing in the dataset such as BMI or vessels that were not findable. These values had to be imputed by K-NN imputation for the linear model in order for the model to work. Forcing the model to calculate missing metrics based on the traits of the k most similar patients can introduce artificial mathematical noise, possibly decreasing the model's performance.

The retrospective nature of the study restricts the analysis to a historical patient cohort where all clinical parameters had already been established. This dependence on pre-existing data introduces a potential selection bias, as individuals with incomplete medical records or those who underwent non-standardized imaging were (partially) excluded from the model training and/or validation process.

A primary technical constraint involves the variation in overall image quality and in availability of contrast-enhanced CT imaging phases within the cohort. The resolution and visibility of the regarding organs and vessels differentiated between patient scans. Furthermore, not all patient scans contained both standardized arterial and portal venous phases. Variations in both image resolution and contrast phase

optimization undermine the consistency and accuracy of both manual and automated measurements. This results in measurement noise, and therefore possibly attenuates the effect of certain parameters.

A limitation of the developed prediction models is not taking the final post-PTA stent diameter into account. From a fluid dynamics perspective, vascular resistance (R) is inversely proportional to the fourth power of the radius (r^4) according to the Hagen-Poiseuille law ($R = \frac{8\eta L}{\pi r^4}$). Consequently, expanding the stent diameter from a baseline of 8 mm to 10 mm induces an exponential reduction in resistance, directly driving the absolute decrease in the post-procedural portal pressure gradient (PPG).

In the cohort, the stent diameter was adjusted dynamically during the intervention based on intraprocedural pressure measurements. If the initial decompression was deemed insufficient, the diameter was upscaled. Because the dataset only captures the final pressure measurements obtained after all adaptations were finalized, the models are blinded to this crucial mechanical modifier. This introduces a structural limitation: the machine learning algorithms are forced to predict a non-linear, variable diameter which is a feedback process based on the PPG during the intervention. While this limits the deterministic physics-based accuracy of the post-PPG prediction, it preserves the models' intended clinical utility as pre-procedural screening tools.

A notable limitation of this study is selection bias. Out of 453 initial patients, only 144 were included in our final dataset. Almost all exclusions resulted from missing pre- or post-TIPS pressure measurements and missing CT-scans. This possibly over-represents relatively stable patients who underwent standardized protocols, while under-representing emergency cases where due to the necessity of fast clinical intervention imaging or pressure measurements were not performed. thus creating a selection bias.

Except from the fact that the initial data is not as consistent as desired, the consistency of the data input is also influenced by software dependency and the specific level of expertise available during parameter acquisition. The determination of organ volumes is directly dependent on the automated segmentation logic of *TotalSegmentator*, meaning any inherent algorithmic inaccuracies are implicitly transferred to the final dataset. Additionally, manual measurements of vascular diameters were conducted by student researchers rather than certified (interventional) radiologists. Although standardized measurement protocols were strictly followed, the lack of extensive clinical experience in vascular radiology introduces a potential risk of both inter- and intra-observer variability. This limitation may ultimately compromise the precision and physiological reliability of the vascular parameters within the predictive models.

The manual diameter measurements were cross-examined only on a random sample basis rather than the entire cohort. This approach introduces a vulnerability to systematic observer bias, where individual variations in manual boundary delineation remain uncorrected. For the machine learning models used (especially XGBoost), this lack of complete data standardization is a significant limitation; the model may undesirably learn patterns linked to differences between observers rather than learn underlying patient physiology, increasing the risk of overfitting.

The study was conducted as a single-center investigation utilizing data exclusively from Erasmus MC. Consequently, the dataset reflects localized clinical guidelines, institutional preferences for TIPS placement and specific scanner hard- and software configurations. Although the current models were evaluated using internal nested cross-validation, external validation in an independent patient population remains essential before clinical implementation can be considered. The lack of multi-center validation limits the external generalizability of both prediction models, as their performance across different hospital protocols, imaging protocols, scanner settings and diverse patient demographics is still unverified.

5.3 Future work

Several opportunities exist to further improve the predictive performance and clinical applicability of the proposed model. First, future studies should include a larger multicentre cohort to increase statistical power and improve the generalizability of the prediction model across different hospitals and patient populations. In addition, external validation using an independent dataset is essential to determine whether the model maintains its performance outside the development cohort.

Furthermore, future data collection would benefit from standardized CT acquisition protocols, including both arterial and portal venous contrast phases for every patient. Standardization of imaging protocols is expected to reduce measurement variability and improve the consistency of anatomical parameter extraction.

Although automatic segmentation of the liver and spleen was successfully applied in this study, vascular diameters were still measured manually. Future developments in automatic vessel segmentation could substantially reduce observer dependency, improve reproducibility and facilitate large scale implementation.

The parameters included in this study were selected based on a preceding systematic review and therefore represent only anatomical features that have previously been investigated in relation to portal pressure. It is possible that other CT-derived anatomical characteristics, which have not yet been described or reported in the literature, may also contain predictive information regarding portal pressure reduction after TIPS. Consequently, the present model may not include all relevant anatomical predictors, potentially limiting its predictive performance. Future studies could explore additional anatomical features using more data-driven feature selection approaches to identify novel predictors of post-TIPS hemodynamic response.

The developed prediction model may also be extended to support additional clinical decisions. For example, future research could investigate whether patient-specific anatomical parameters can assist in selecting the optimal TIPS stent diameter before the procedure, in order to balance the expected portal pressure reduction against the risk of hepatic encephalopathy.

Finally, the current application could be expanded to compare the predicted hemodynamic effects of different treatment strategies, such as TIPS placement and splenic embolisation. Such an extension could provide clinicians with additional patient-specific information to support individualized treatment selection and contribute to more personalized management of portal hypertension.

6 Conclusion

This study aimed to develop a clinically applicable patient-specific prediction model for portal pressure reduction after Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement using routinely available CT-derived anatomical parameters and clinical variables. Two machine learning approaches were evaluated: an interpretable Elastic Net linear regression model and a non-linear XGBoost model.

The Elastic Net model achieved the best predictive performance, outperforming the more complex XGBoost model. Nevertheless, the overall predictive accuracy remained modest, with an average prediction error of approximately 2 mmHg and a low explained variance. These findings indicate that static anatomical CT-derived parameters alone are insufficient to accurately predict the individual hemodynamic response after TIPS placement. The results could suggest that additional physiological factors, such as portal blood flow, collateral circulation and vascular resistance, play an important role in determining post-procedural portal pressure.

Despite its limited predictive performance, this study demonstrates that routinely available anatomical CT parameters contain clinically relevant information regarding portal pressure reduction after TIPS. Furthermore, the use of an interpretable linear model provides insight into the relative contribution of individual anatomical variables and offers a transparent alternative to more complex machine learning approaches.

At present, the developed model is not sufficiently accurate to support independent clinical decision-making. However, it provides a valuable foundation for future research aimed at improving patient-specific prediction of treatment response. Expanding the model with larger multicentre cohorts, standardized CT acquisition protocols, automated vessel segmentation and external validation may ultimately result in a clinically applicable tool that supports personalized treatment planning and facilitates comparison between TIPS and alternative interventions such as splenic artery embolisation.

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A Formulas

$$MAE = \frac{1}{n}\sum_{i=1}^{n}|y_i - \hat{y}_i| \tag{2}$$

Where:

- n: Total number of patients in the test set.
- y_i: The actual measured post-TIPS PPG for patient i.
- $\hat{y}_i$: The predicted post-TIPS PPG for patient i.

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2} \tag{3}$$

Where:

- n represents the total number of patients evaluated within the respective test fold.
- y_i The actual measured post-TIPS PPG for patient i.
- $\hat{y}_i$ The predicted post-TIPS PPG for patient i.
- $(y_i - \hat{y}_i)$ represents the residual error for an individual patient case.

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2} \tag{4}$$

Where:

- y_i: The actual measured post-TIPS PPG for patient i.
- $\hat{y}_i$: The predicted post-TIPS PPG for patient i.
- $\bar{y}$: The mean of the actual measured post-TIPS PPG for all patients.
- $\sum(y_i - \hat{y}_i)^2$: The sum of squares of residuals (the error of the model).
- $\sum(y_i - \bar{y})^2$: The total sum of squares (the total variance in the data).

B Manual segmentation protocol

C Protocol for manual segmentation per anatomical structure

Protocol for manual segmentation per anatomical structure

General measurement method

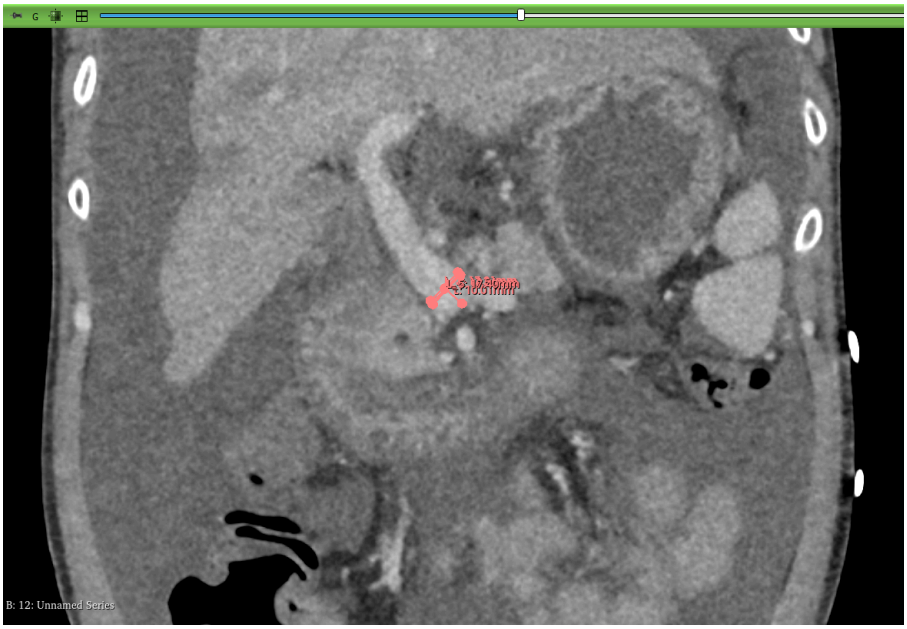
For all vascular structures, the following standardized measurement protocol is applied:

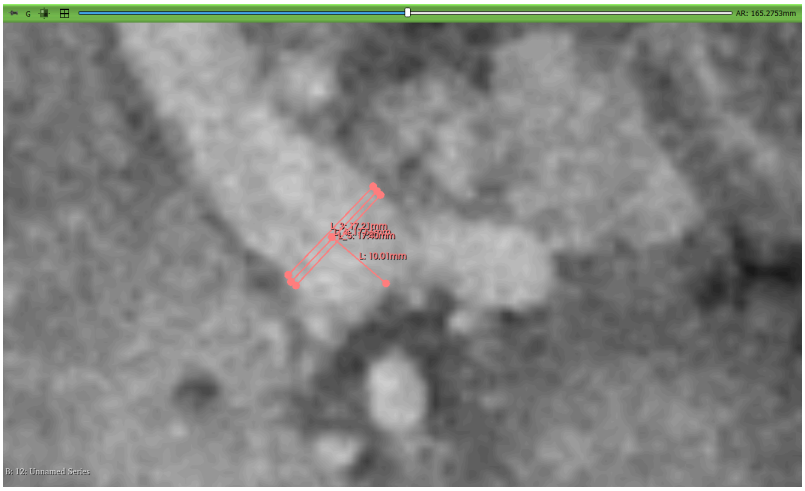
- The vessel diameter is measured perpendicular to the longitudinal axis of the vessel using multiplanar reconstruction (MPR).
- Diameters are measured from inner wall to inner wall.
- Three measurements are obtained around the predefined anatomical landmark, and the mean value is used for analysis.
- The image is magnified as much as possible so that the vessel occupies a large proportion of the screen, maximizing measurement accuracy.

1 Vena porta

Measurement location

- Measurements are performed on portal venous phase CT images, when available.
- The diameter is measured 1 cm distal to the confluence of the splenic vein and superior mesenteric vein, within the main portal vein trunk.
- The measurement is performed perpendicular to the vessel axis in the coronal plane, using the slice in which the vessel diameter appears largest.

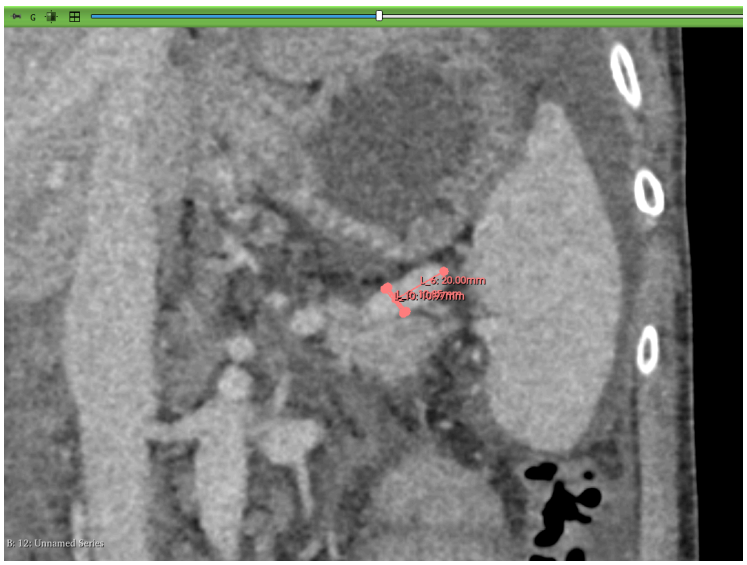


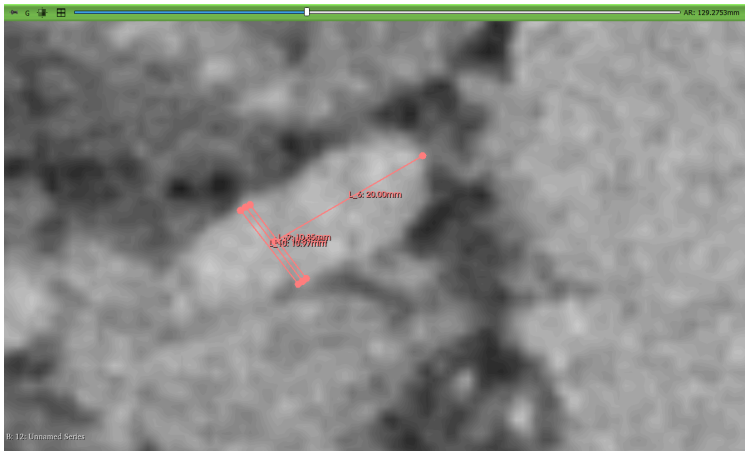


2 Vena lienalis

Measurement location

- Measurements are performed on portal venous phase CT images, when available.
- The diameter is measured 2 cm distal to the splenic hilar venous confluence, where the hilar tributaries merge into the main splenic vein.
- The measurement is performed perpendicular to the vessel axis in the coronal plane, using the slice in which the vessel diameter appears largest.

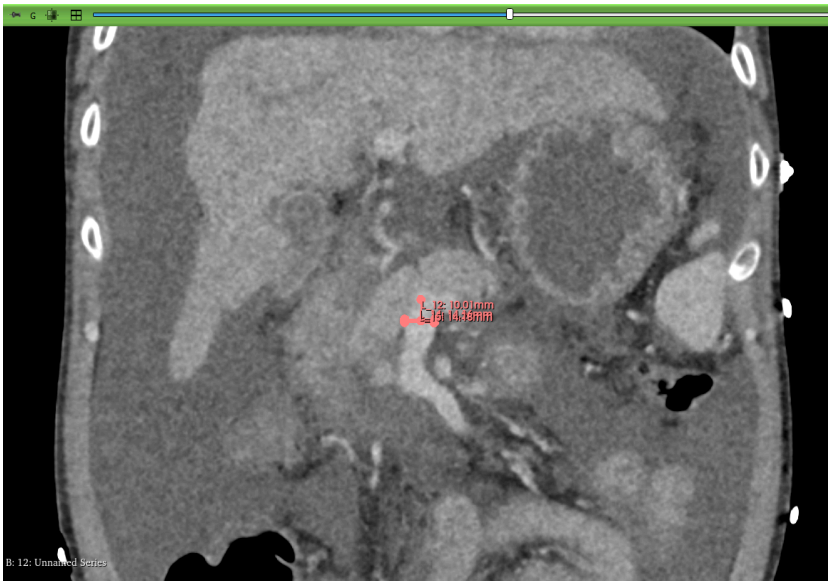


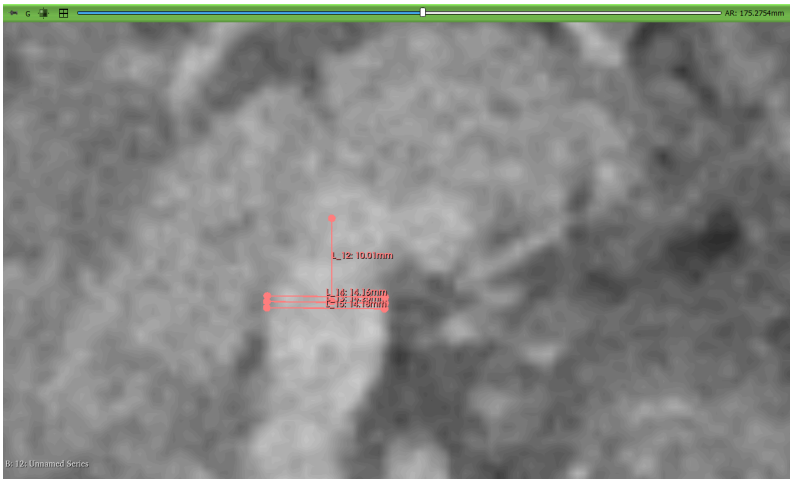


3 Vena mesenterica superior

Measurement location

- Measurements are performed on portal venous phase CT images, when available.
- The diameter is measured 1 cm proximal to the confluence with the splenic vein.
- The measurement is performed perpendicular to the vessel axis in the coronal plane, using the slice in which the vessel diameter appears largest.

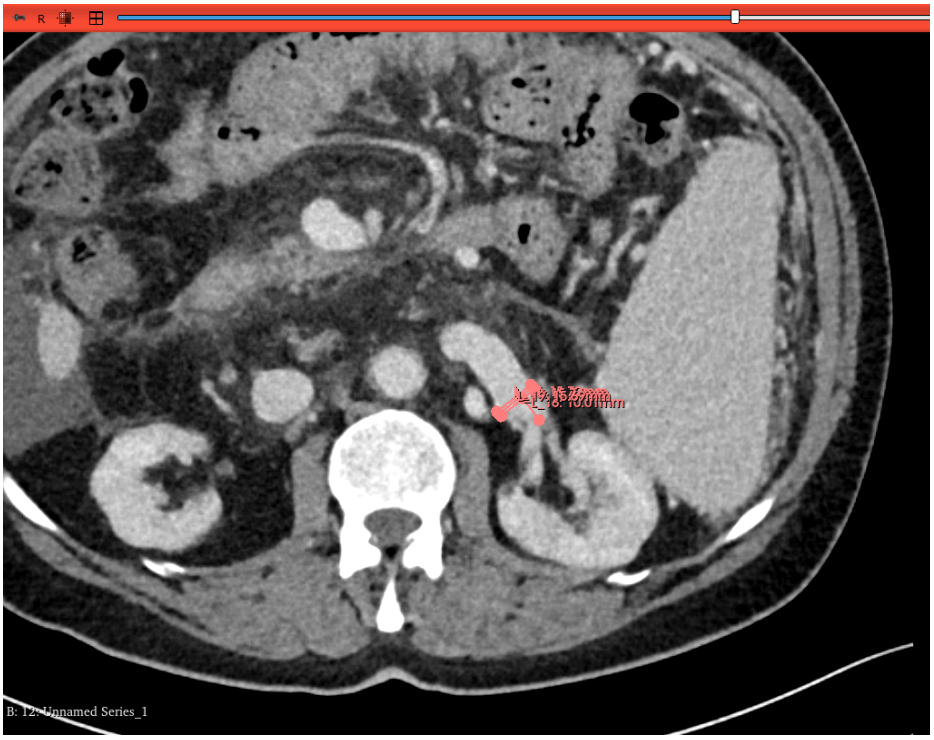


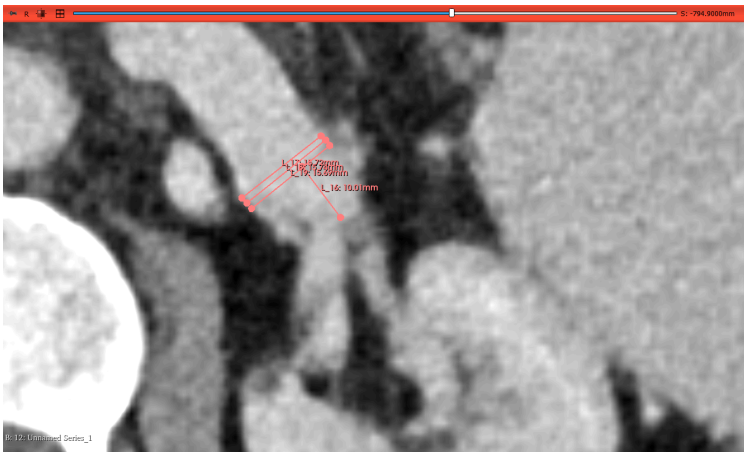


4 Vena renalis sinistra

Measurement location

- Measurements are performed on portal venous phase CT images, when available.
- The diameter is measured 1 cm distal to the renal hilum within the main trunk of the left renal vein.
- The measurement is performed perpendicular to the vessel axis in the axial plane, using the slice in which the vessel diameter appears largest.


B: 12: Unnamed Series_1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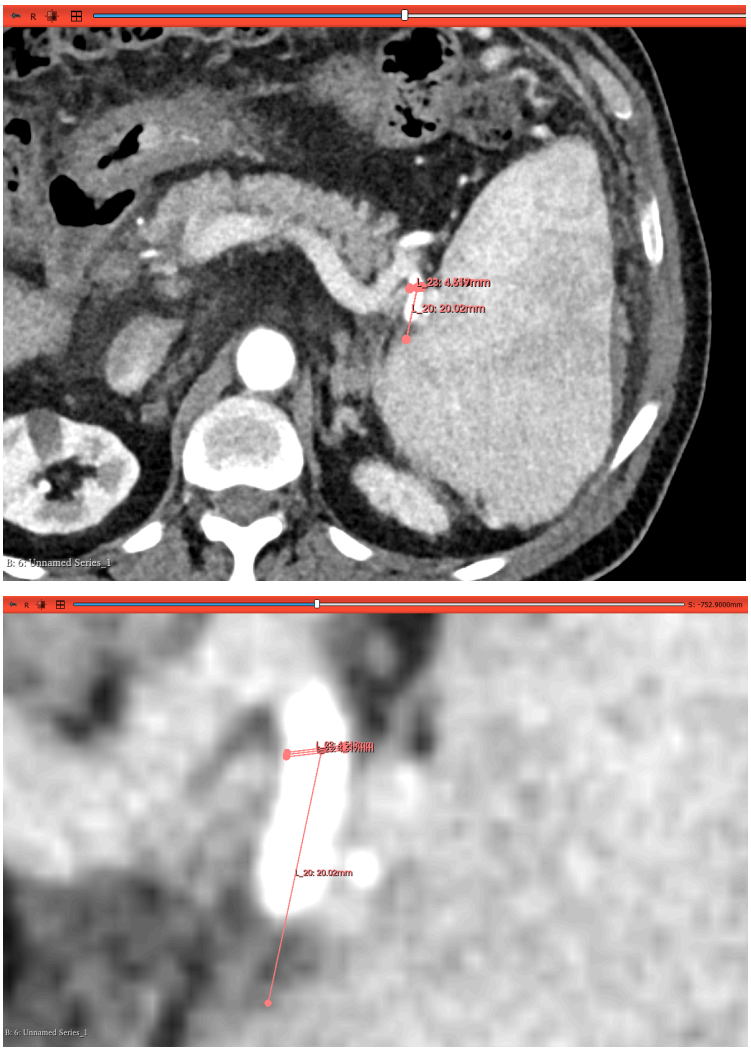
5.5 Arteria lienalis

Measurement location

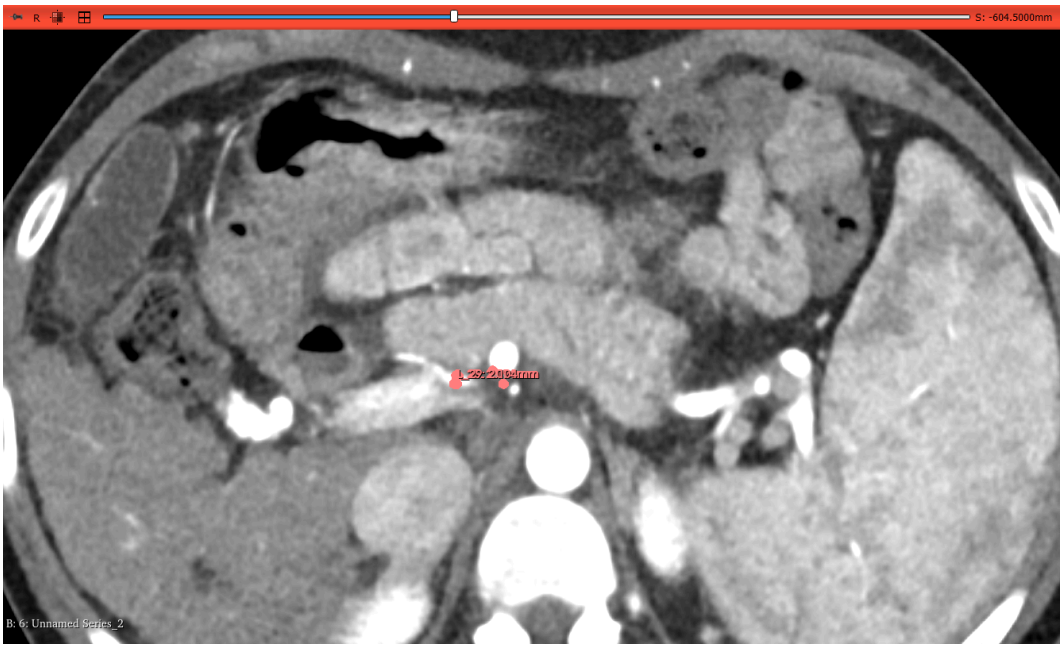
- Measurements are performed on arterial phase CT images, when available.
- The diameter is measured 2 cm proximal to the splenic hilum within the main splenic artery.
- The measurement is performed perpendicular to the vessel axis in the axial plane, using the slice in which the vessel diameter appears largest.

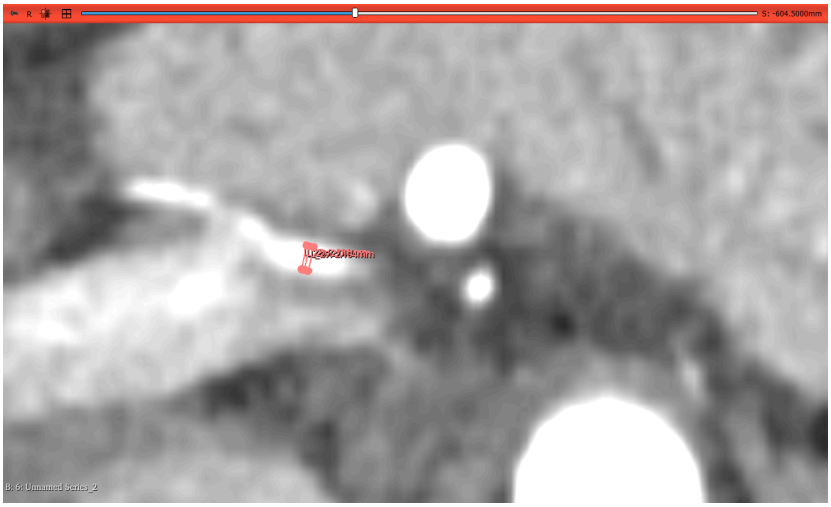


6 Arteria hepatica proper

Measurement location

- Measurements are performed on arterial phase CT images, when available.
- The diameter is measured 1 cm distal to its origin from the common hepatic artery, before the first arterial bifurcation.
- The measurement is performed perpendicular to the vessel axis in the axial plane, using the slice in which the vessel diameter appears largest.





D Original Project Description

The original project description, as provided by the supervisors at the start of the project, is included below.

Project title

The role of splenic artery embolisation in treatment of portal hypertension related disease

1. Background

Patients with liver disease often develop complications due to increased vascular resistance caused by hepatic fibrosis, resulting in impaired blood outflow from the abdominal organs through the portal vein. Consequently, portal venous pressure increases, which may lead to ascites and the development of gastric and esophageal varices that are at risk of bleeding.

Current treatment options include the placement of a *Transjugular Intrahepatic Portosystemic Shunt (TIPS)*, creating an intrahepatic bypass to decompress the portal venous system. A less frequently applied alternative is splenic artery embolisation (coiling), which reduces blood inflow into the portal circulation by occluding the splenic artery, thereby lowering portal pressure.

The available literature regarding the expected effect of splenic artery embolisation on portal pressure and clinical outcomes remains limited. Existing studies, performed in relatively small patient cohorts, demonstrated a linear relationship between portal pressure reduction after temporary splenic artery occlusion and spleen size. By performing 3D segmentation of the spleen, these findings can be applied to a historical TIPS cohort to model the portal pressure reduction that could theoretically be achieved by splenic artery embolisation.

2. Objective of the literature review (KTO-A)

What is the expected reduction in portal venous pressure that can be achieved by splenic artery embolisation, and how does this compare to the pressure reduction achieved with TIPS? Can splenic artery embolisation therefore be considered a valuable alternative to TIPS?

3. Objective of the research project (KTO-B)

Formulate an evidence-based recommendation regarding the potential role of splenic artery embolisation in the treatment of portal hypertension and related complications such as ascites and variceal bleeding.

This project aims to:

- Perform 3D segmentation of spleen volumes in a historical TIPS cohort.
- Model the expected portal pressure reduction after splenic artery occlusion based on previously published invasive pressure measurements.
- Compare the theoretically achievable pressure reduction after splenic artery embolisation with the observed pressure reduction after TIPS.
- Evaluate whether splenic artery embolisation could theoretically provide a clinically relevant alternative to TIPS.

4. Intended outcome

Development of a model estimating the portal pressure reduction achievable with splenic artery embolisation and evaluation of its potential clinical relevance compared with TIPS.

5. Facilities

The required facilities and patient data were already available through Erasmus MC.

6. Supervisors

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E Systematic Literature Review

The literature review submitted during Block 4A is included in this appendix without modifications.

CT-Based Anatomical Parameters Associated With Portal Pressure and Hemodynamics in Portal Hypertension: A Systematic Review and Meta-Analysis

KTO-AS25011, Miltembolisatie-EMC, GR25018

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1 Abstract

Background and Objectives Portal hypertension is a severe clinical condition caused by increased vascular resistance, often leading to complications such as variceal bleeding and ascites. When pharmacological treatment is not sufficient, interventions like the Transjugular Intrahepatic Portosystemic Shunt (TIPS) or alternatives such as splenic embolisation may be considered. This systematic review aims to evaluate how anatomical parameters measurable on CT are physiologically and mathematically related to portal pressure.

Methods A systematic literature search was conducted in the PubMed and Scopus databases for relevant studies published up to April 30, 2026. Study quality was assessed using a custom standardized scoring rubric. Data synthesis utilized a vote-counting method and a meta-analysis of Pearson correlation coefficients if sufficient data was available.

Results In total 36 studies were included. Qualitative synthesis indicated that increased spleen volume, a higher spleen/liver ratio, and larger diameters of the portal vein and splenic vein were most consistently correlated with higher portal pressure. The meta-analysis showed significant positive correlations between the hepatic venous pressure gradient (HVPG) and 3 variables; spleen volume ($r = 0.64$, 95% CI [0.49, 0.75]), portal vein diameter ($r = 0.43$, 95% CI [0.23, 0.60]), and splenic vein diameter ($r = 0.42$, 95% CI [0.14, 0.63]).

Discussion and conclusion Larger organ volumes and venous diameters on CT correlate with increased portal pressure. Despite methodological heterogeneity and purely correlational evidence, these anatomical parameters hold potential for developing non-invasive prediction models for hemodynamic changes following interventions.

2 Introduction

Portal hypertension is caused by increased hepatic vascular resistance, most commonly due to liver cirrhosis. In portal hypertension, there is an increased Hepatic Venous Pressure Gradient (HVPG >5 mmHg), which can lead to severe complications such as refractory ascites, hepatorenal syndrome, and variceal bleeding when exceeding 10 mmHg. [1].

When pharmacological treatment fails, the standard procedure is the placement of a 'Transjugular Intrahepatic Portosystemic Shunt' (TIPS). During this procedure, a bypass is created percutaneously within the liver to divert part of the blood flow directly from the portal vein to the hepatic vein.

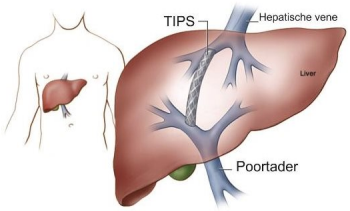


Figure 1: Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Although TIPS treatment is effective, the procedure is associated with significant risks, such as procedural burden and an increased risk of hepatic encephalopathy, which is accompanied by confusion, drowsiness, and concentration problems. [2]

There is also increasing interest in alternative treatment options, such as (partial) splenic embolization, in which blood supply to the spleen is reduced in order to decrease portal inflow and thereby lower portal pressure. Although potentially less invasive, limited evidence exists regarding its pressure reduction and effectiveness compared with TIPS.

Because both TIPS and splenic embolization aim to alter portal hemodynamics, there is increasing interest in identifying anatomical predictors that may help estimate portal pressure and treatment response in a patient-specific manner. CT-based measurements are routinely available in clinical practice and may therefore provide a more clinically applicable alternative to complex hemodynamic measurements.

Several studies investigated CT-based anatomical parameters in relation to portal pressure and hemodynamics. [3]. However, the reported associations remain heterogeneous and no clear overview exists regarding which anatomical parameters are most strongly related to portal hypertension severity and pressure reduction after intervention. A systematic evaluation of these anatomical predictors may improve understanding of portal hemodynamics and support the development of future patient-specific treatment strategies.

Therefore, this systematic review aims to evaluate how anatomical parameters measurable on CT, including spleen volume, liver volume, and portal vascular diameters, are physiologically and mathematically related to portal pressure in patients with portal hypertension.

3 Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [4].

3.1 Literature search

A systematic search was conducted using the PubMed and Scopus databases to include studies published no later than April 30, 2026. The search queries were constructed by combining keywords, synonyms and Medical Subject Headings (MeSH) related to four relevant domains:

- anatomical parameters (e.g. Spleen volume, vessel diameters)
- measurement (e.g. diameter, size or 3D segmentation)

- portal pressure (e.g. Portal venous pressure, HVPG)
- clinical population (e.g. liver cirrhosis, portal hypertension)

The full search strategies for both databases can be found in Appendix A.

The authors independently performed title and abstract screening, and full-text screening on pre-set inclusion criteria, with 2 authors reviewing each article. Any inconsistencies between the reviewers were resolved by thorough discussion between the reviewers. After the articles were screened based on their abstracts and titles, a full-text review was done with the same inclusion criteria. No snowballing was applied in the search for articles.

3.2 Inclusion criteria

1. Includes human adult patients with cirrhosis, chronic liver disease or portal hypertension.
2. Includes quantitative relationship between anatomical parameters and portal pressure.
3. Article is an original study (excluding abstracts, letters, reviews, case-reports, and meta-analyses).
4. Full text available.
5. Article is written in English or Dutch.

3.3 Quality assessment

To evaluate the methodological strength and risk of bias of the studies included in this systematic review, a standardized quality assessment was performed (table 1). Standard risk-of-bias tools such as ROBINS-I or the Newcastle-Ottawa Scale were not used because the included studies showed substantial methodological heterogeneity and frequently focused on imaging correlations rather than intervention outcomes. Therefore, this custom quality assessment rubric was developed to better evaluate methodological aspects specifically relevant to imaging-based anatomical and hemodynamic studies. This assessment ensures that the extracted data regarding the relationship between anatomical parameters and portal pressure is clinically valid. Any study with a methodological score of 10 or lower will be excluded from this review because of poor methodological quality.

Studies were scored across seven methodological domains on a scale from 0 to 3.

Table 1: Quality Assessment Rubric for Literature Selection

Criterion	**Score 3 (Excellent)**	**Score 2 (Good)**	**Score 1 (Moderate)**	**Score 0 (Weak)**
Cohort Size (N)	$N > 150$	$N = 100 - 149$	$N = 50 - 99$	$N < 50$
Study Design	-	Prospective	Retrospective	-
Reference Standard	Invasive HVPG (gold standard)	Invasive Portal Venous Pressure (PVP)	Indirect markers	No objective pressure measurement
Anatomical Measurement Method	3D volumetry (automatic segmentation)	Manual segmentation (planimetry)	2D lengths / diameters (e.g., spleen length)	Visual estimation only (nodularity/ascites)
Statistical Validation	External validation cohort	Internal validation cohort	Correlation analysis only	No statistical foundation
Reproducibility	Method is clearly and reproducibly described	Method is clearly described to a certain extent	Method is partially reproducibly described	Not reported
Imaging	CT	MRI	Ultrasound	Other

3.4 Data extraction

Data extraction was conducted systematically using a standardized extraction form to evaluate how specific anatomical parameters relate physiologically and mathematically to portal pressure and hemodynamics. No automation tools were used in the data collection process. Data collection was done independently by the authors with one author per article.

From each included study, data across these domains were extracted:

- **Study characteristics:** study design, patient population details, research question.
- **Direct or indirect variables:** Whether the variable had a direct effect on a pressure gradient.
- **Measurement modalities:** CT, MRI, ultrasound or other measurement techniques.
- **Anatomical parameters:** Quantitative measurements of relevant anatomical structures and their influence on portal pressure.
- **Hemodynamic variables:** Specific observations regarding portal hemodynamics and portal pressure measurements.
- **Mathematical relationships:** Any mathematical or statistical relationship, including specific formulas, correlation coefficients, p-values and categorizations of parameters.

3.5 Data synthesis and statistical analysis

Due to significant methodological heterogeneity regarding measurement modalities, statistical metrics and patient populations, a dual approach to data synthesis was used.

For all included anatomical parameters, a qualitative vote-counting analysis was conducted. Because many included studies reported only qualitative associations or lacked comparable statistical metrics, a vote-counting synthesis allowed consistent evaluation of the direction and frequency of reported associations across a broad range of anatomical parameters. For every study, each mentioned parameter that is measurable on CT was assessed for statistical correlation. A standardized metric based on the direction of effect was utilized. A vote-counting method was applied to synthesize the number of studies that showed a statistically significant positive, negative, or non-significant association. A p-value less than 0.05 was deemed significant.

When at least 4 studies provided correlation coefficients (Pearson's r) for a specific anatomical parameter, a meta-analysis was performed to provide an overview of the existing evidence and the magnitude of the correlation coefficients between HVPG and the anatomical parameter. The amount of 4 was chosen as a lower number of studies would limit the ability to accurately estimate between-study variance (τ^2), which can lead to unstable pooled estimates. The meta-analysis was performed using the software RStudio.

As Pearson correlation coefficients (r) are bounded between -1 and +1, their sampling distribution becomes skewed as the correlation deviates from zero. To stabilize variance and minimize the chance of statistical bias, all correlation coefficients were transformed into Fisher's z scores prior to analysis. The Fisher's z transformation and standard error (SE) for each transformed score were calculated using the formula:

$$Z = \frac{1}{2} \ln \left(\frac{1+r}{1-r} \right)$$

Fisher's z-transformation

$$SE = \frac{1}{\sqrt{n-3}}$$

StandardError (SE)

A random-effects model was chosen for the meta-analysis. Forest plots were utilized to synthesize and visualize the individual study estimates, corresponding 95% confidence intervals (CIs), study weights,

and the final pooled effect size within a single graphic. Finally, the final pooled Fisher's z scores and their corresponding 95% CIs were transformed back to Pearson's r correlation coefficients for better interpretation.
To evaluate the reliability of the pooled estimates and identify potential influential studies, a leave-one-out sensitivity analysis was performed for each anatomical parameter.

4 Results

4.1 Search results and study characteristics

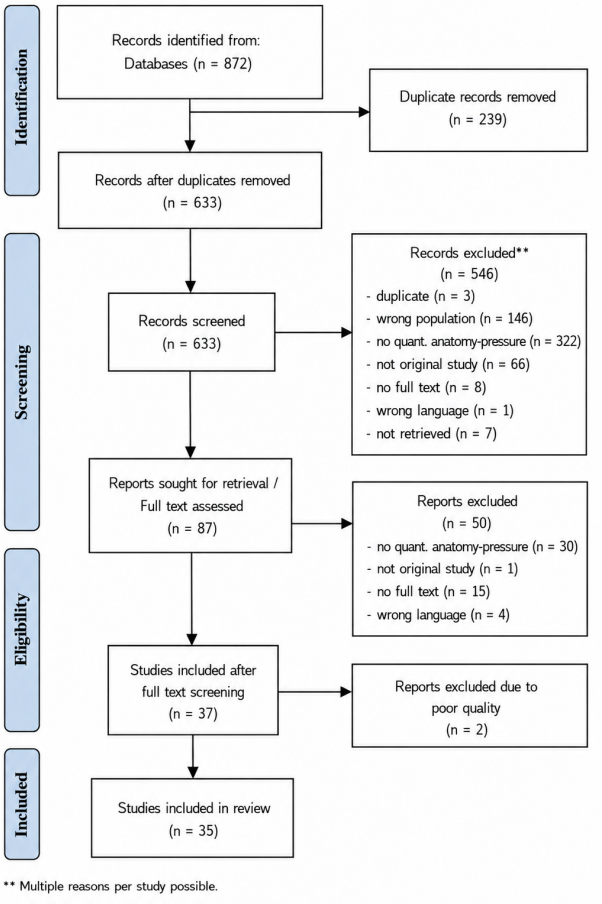


Figure 2: Flow diagram of article screening and study inclusion for the systematic review.

The literature search resulted in 591 articles from Scopus and 281 articles from PubMed. 239 of these were duplicates. After title and abstract screening and full-text review and quality assessment, 35 articles were included in this systematic review. Figure 2 shows the flowchart of the studies from the search query until inclusion.

Quality assessment: The overall methodological quality of the included studies varied, with total quality scores ranging from 10 to 18 points (Max=20 points). A detailed breakdown of the quality assessment for each study is shown in Table 2. 2 studies were excluded from the review because of poor methodological quality.

Table 2: Quality Assessment of Included Studies

Study (Author, Year)	Cohort Size	Study Design	Msmt portal pressure	Msmt anatomic variable	Stat. Validation	Reproducibility	Imaging	Total Score
Shanka et al., 2026 [5]	3	1	3	1	2	3	1	**14**
Gao et al., 2026 [6]	3	1	2	3	2	3	3	**17**
Chen et al., 2025 [7]	2	1	3	3	2	3	3	**17**
Wang et al., 2023 [8]	0	1	2	3	3	3	3	**15**
Heo et al., 2023 [9]	3	1	2	3	2	3	3	**17**
Romero-Cristobal et al., 2023 [10]	3	0	3	3	3	3	3	**18**
Kennedy et al., 2022 [11]	0	2	3	2	2	3	2	**14**
Romero-Cristobal et al., 2022 [12]	3	1	3	3	2	3	3	**18**
He et al., 2022 [13]	0	2	2	2	1	2	3	**12**
Altinmakas et al., 2022 [14]	1	2	3	2	1	3	2	**14**
Ishikawa et al., 2021 [15]	1	1	3	3	1	3	3	**15**
Pieper et al., 2021 [16]	3	2	1	1	3	3	3	**16**
Yao et al., 2020 [17]	1	1	3	1	1	3	1	**11**
Mohapatra et al., 2019 [18]	0	1	2	1	1	3	3	**11**
Etzion et al., 2018 [19]	1	1	3	2	1	3	3	**14**
Sartoris et al., 2018 [20]	3	1	3	2	3	3	3	**18**
Tseng et al., 2018 [21]	1	1	3	2	1	3	3	**14**
Simón-Talero et al., 2018 [22]	3	1	1	2	1	2	3	**13**
Kihira et al., 2016 [23]	2	1	3	3	2	3	3	**17**
Zhang et al., 2016 [24]	1	2	2	2	2	3	3	**15**
Yan et al., 2015 [3]	3	1	3	2	2	3	3	**17**
Iranmanesh et al., 2014 [25]	2	1	3	2	3	3	3	**17**
Lee et al., 2014 [26]	2	1	3	1	1	3	3	**14**
Palikhe et al., 2013 [27]	1	2	2	1	2	3	3	**12**
Hayashi et al., 2012 [28]	0	2	2	3	1	3	3	**14**
Singh et al., 2011 [29]	0	2	2	2	1	3	3	**13**
Luca et al., 2006 [30]	0	2	2	2	1	3	3	**13**
Haag et al., 1999 [31]	2	1	3	2	3	3	1	**15**
Sharma et al., 1997 [32]	1	1	1	2	1	2	3	**11**
Jalan et al., 1996 [33]	1	1	3	2	3	3	3	**16**
Takagi et al., 1994 [34]	1	2	2	3	1	3	3	**15**
Dubois et al., 1993 [35]	1	2	3	1	1	2	1	**11**
Peng et al., 1993 [36]	0	2	2	1	1	3	1	**10**
Vilgrain et al., 1990 [37]	1	2	3	1	1	3	1	**12**
Zoli et al., 1985 [38]	0	2	2	1	1	3	1	**10**
Valla et al., 1984 [39]	1	2	2	1	1	3	1	**11**
Yamauchi et al., 1970 [40]	1	2	2	2	1	3	1	**12**

4.2 Results based on study methodology

Parameter	Significant direct	Significant indirect	Not significant	Significant correlation	Quantitative correlation
Spleen volume	12	4	2	Higher volume → higher portal pressure	
Liver volume	4	1	6	Higher volume → higher portal pressure	
Spleen/liver ratio	6	1		Spleen/liver ratio higher → stronger pressure reduction, Spleen/liver ratio higher → HVPG higher	Spleen/liver ratio > 0.5 predicts strong pressure reduction (>20%)
Diameter portal vein	5	4	2	Higher pressure → greater diameter	
Diameter splenic vein	7	1	3	Higher pressure → greater diameter, Higher splenic vein diameter → higher pressure reduction	
Diameter superior mesenteric vein	3		1	Reduction in caliber → reduction in WHVP	
Diameter arteria splenica	1			Higher pressure → greater diameter	Linear relation between arteria splenica radius and portal pressure in portal hypertension: P=0.36×r+2.6
Diameter left renal vein	1			Higher pressure → greater diameter	
Diameter common hepatic artery		1		Higher pressure → greater diameter	
Esophageal varices	1			higher pressure → more varices	
Gastric varices			1	No correlation	
Paraesophageal varices			1	No correlation	
Portal vein/splenic vein ratio	1			Stronger portal hypertension, higher ratio	
Superior mesenteric vein/splenic vein ratio	1			Stronger portal hypertension, higher ratio	
Ascites	2	2		Higher portal pressure → more ascites	
Spleen volume/BMI ratio	1			Higher ratio → higher HVPG	
Liver volume/BMI ratio	1			Higher ratio → higher HVPG	
Spontaneous PortoSystemic Shunt (SPSS)	1	3		Higher pressure → more shunts	
Diameter varicose veins			1	No correlation	
Common hepatic channel (CCh) diameter		1		Diameter decreases after TIPS → indirectly lower pressure	

Table 3: Overview of parameters associated with portal pressure and hemodynamics from the literature.

Table 4: Mathematical formulas for predicting portal pressure found in literature

Author(year)	**Mathematical correlations**
Tseng et al. (2018)	$\text{HVPG} = 18.726 - 0.324 \cdot (\text{albumin}) + 1.57 \cdot (\text{APRI}) + 0.004 \cdot (\text{liver volume})$
Zhang et al. (2016)	$\text{PVP (mmHg)} = 2.529 + 1.572 \cdot \text{SVD (mm)} + 0.231 \cdot \frac{\text{SV}}{\text{BMI}} (\cdot 10^4\ \text{cm}^5/\text{kg}) + 3.44 \cdot \text{APRI}$
Yan et al. (2015)	$\text{HVPG score} = 13.651 - 6.187 \cdot \ln\left(\frac{\text{liver volume}}{\text{spleen volume}}\right) + 2.755 \cdot \text{varices score}^*$
Iranmanesh et al. (2014)	$\text{HVPG score} = 17.37 - 4.91 \cdot \ln(\text{liver/spleen volume ratio}) + 3.8 \cdot$ [if presence peri-hepatic ascites]

Note: APRI = Aspartate aminotransferase-to-platelet ratio index. SVD = Splenic Vein Diameter. SV = Spleen Volume. BMI = Body Mass Index. *Varices score: small = 1; big = 2.

The results of the vote-counting synthesis (table 3) demonstrated that several anatomical parameters are associated with portal pressure and portal hypertension severity. Among all investigated variables, spleen volume was the most consistently reported parameter, with the majority of studies demonstrating a significant positive correlation between increasing spleen volume and higher portal pressure. Larger diameters of the portal vein and splenic vein were also frequently associated with increased portal pressure. In addition, higher spleen-to-liver ratios were linked to both higher HVPG and stronger pressure reduction after intervention.

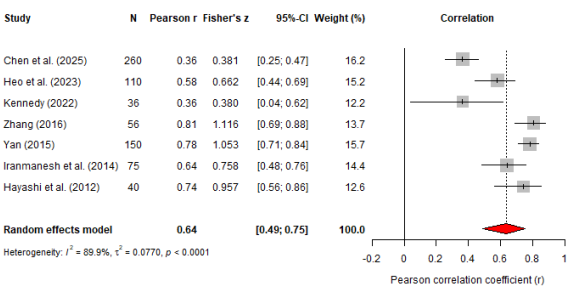
Several indirect markers, including ascites, spontaneous portosystemic shunts (SPSS), and histological liver lesions, were also associated with more advanced portal hypertension. However, not all parameters showed consistent significance, as gastric varices, paraesophageal varices, and variceal diameter were reported as non-significant.

Mathematical relationships relating portal pressure with several markers found during the literature search are shown in Table 4.

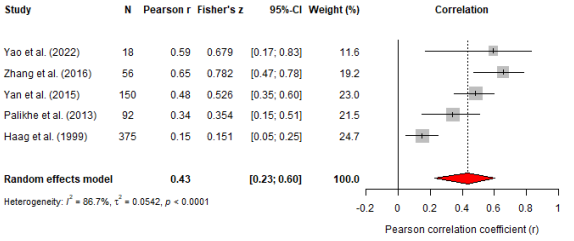
Overall, the literature suggests that spleen-related parameters and portal venous diameters are the most promising anatomical predictors of portal hemodynamics.

4.3 Meta-analysis

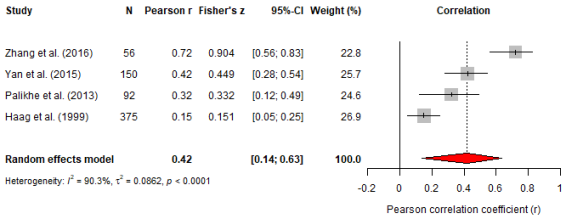
A meta-analysis was conducted to evaluate the pooled correlations between three CT-measurable anatomical parameters and the hepatic venous pressure gradient (HVPG). The results of these analyses are presented in the forest plots in Figure 3.



(a) Correlation between spleen volume and HVPG.



(b) Correlation between portal vein diameter and HVPG.

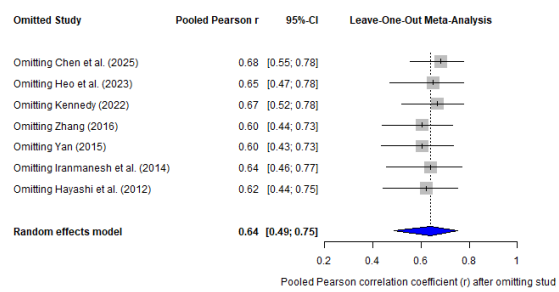


(c) Correlation between splenic vein diameter and HVPG.

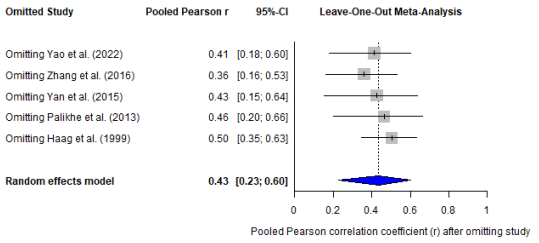
Figure 3: Forest plots showing correlations between anatomical parameters and hepatic venous pressure gradient (HVPG).

The pooled analysis revealed that spleen volume has the strongest positive correlation with portal pressure ($r = 0.64$, 95%-CI : $[0.49; 0.75]$), indicating it as the most robust anatomical predictor between the three assessed parameters. Both portal vein diameter ($r = 0.43$, 95%-CI : $[0.23; 0.60]$) and splenic vein diameter ($r = 0.42$, 95%-CI : $[0.14; 0.63]$) also demonstrated significant, moderately positive correlations with HVPG.

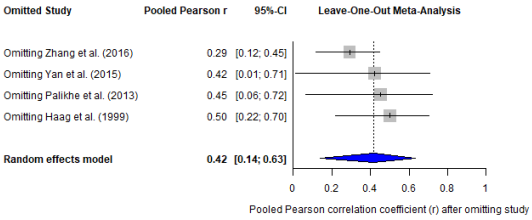
Importantly, while all three parameters consistently demonstrated that larger anatomical dimensions are associated with elevated portal pressure, considerable statistical heterogeneity was observed across all models, including spleen volume ($I^2 = 89.9\%$), portal vein diameter ($I^2 = 86.7\%$), and splenic vein diameter ($I^2 = 90.3\%$). This high heterogeneity suggests that the magnitude of the correlations varies considerably between the individual studies.



(a) Sensitivity analysis spleen volume and HVPG.



(b) Sensitivity analysis portal vein diameter and HVPG.



(c) Sensitivity analysis splenic vein diameter and HVPG.

Figure 4: Forest plots showing the sensitivity analysis of the included studies.

The sensitivity analysis shows that all the 95% confidence intervals of the meta-analysis remained positive when a study was excluded from the analysis. This indicates that all volumetric parameters included in the meta-analysis are not disproportionately driven by a single study and therefore did not alter the primary findings of the meta-analysis.

5 Discussion

This systematic review evaluated what parameters measurable on CT statistically correlate with portal venous pressure. CT offers very simple, reproducible and standardized 3D anatomical data. The analyzed parameters included spleen volume, liver volume, spleen-to-liver ratio, portal vein diameter, splenic vein diameter, superior mesenteric vein diameter, splenic artery diameter, left gastric vein, esophageal varices, portal vein/splenic vein ratio, superior mesenteric vein/splenic vein ratio, ascites, spleen volume/BMI ratio, liver volume/BMI ratio, collateral veins, spontaneous portosystemic shunts (SPSS), common hepatic artery diameter, variceal vein diameter, and common hepatic channel (CCh) diameter. These parameters are relevant for integration into a mathematical prediction model about portal pressure change after TIPS.

Physiologically, the positive correlation between spleen volume and HVPG aligns with the mechanism of backward venous congestion. The spleen acts as a compliant reservoir that enlarges as portal resistance increases. This can explain why spleen volume correlates more strongly with portal pressure than liver volume. The cirrhotic liver typically becomes fibrotic and either remains rigid or shrinks. Interestingly, the portal vein and splenic vein showed only moderate correlations. A possible explanation for this could be that the vein potentially reaches a maximum dilation and cannot dilate further. Additionally, the formation of portosystemic shunts can partially decompress the portal system, reducing vein diameter despite elevated pressure. It is important to emphasize that these relationships are correlations. It is debatable whether splenic enlargement is solely a consequence of backward congestion, or if increased splenic blood flow actively causes portal hypertension.

This synthesis has several limitations, inherent to the available literature, such as the wide variety of imaging protocols and measurement techniques used across the included studies. The main limita-

tion of this review is that for many parameters, insufficient data was available across studies to perform a meta-analysis. Consequently, for these variables we could not account for the magnitude of the effect size or differences in sample sizes. Furthermore, an important consideration is the high statistical heterogeneity observed across all meta-analysis models ($I^2 > 85\%$, $p < 0.0001$). This heterogeneity can partially be explained by differences in underlying etiologies and methodological differences, such as varying time intervals between the CT scan and the portal pressure measurement, and differences in HVPG measurement techniques. The heterogeneity in methodologies between studies introduces a degree of bias. Despite this heterogeneity, the performed meta-analysis demonstrated moderate pooled positive correlations between spleen volume, portal vein diameter, splenic vein diameter, and HVPG, supporting the consistency of these anatomical associations across studies. The sensitivity analysis did not find any studies that disproportionately altered the correlations, indicating some robustness in the observed correlations.

We also have to take a closer look at both retrospective bias and selection bias, both of which could be present within this study. Because many included studies used retrospective cohorts, data availability depended on previously acquired imaging and segmentations, which may result in incomplete datasets. In addition, selection bias may occur since only patients with available CT imaging and portal pressure measurements were included. To reduce these effects, strict inclusion and exclusion criteria and a standardized quality assessment were applied.

An important consideration is that the observed relationships represent correlations rather than causal effects. Although parameters such as spleen volume and portal venous diameters showed significant correlations with portal pressure, it remains unclear whether these variables contribute to increased portal pressure or merely reflect changes as a result of it.

Future research should focus on performing more prospective studies evaluating the correlation between HVPG and anatomical parameters where the current body of evidence is insufficient to perform a meta-analysis. Furthermore, heterogeneity could potentially be reduced by strictly grouping studies by etiology of portal hypertension and measurement methodologies.

6 Conclusion

This systematic review concludes that anatomically based parameters are associated with portal pressure. The most recurring and consistently correlated parameters identified in both the vote-counting synthesis and meta-analysis were spleen volume (3a), portal vein diameter (3b), and splenic vein diameter (3c). Several additional parameters were also identified that were suggested to be either directly or indirectly related to portal pressure. In general, the trends observed indicate that increased organ volumes and larger venous diameters are associated with increased portal pressure. However, not all parameters proved to be equally significant across all included studies. These parameters could be clinically relevant for the development of a portal pressure prediction model based solely on anatomical characteristics present on CT imaging combined with an initial portal pressure measurement.

These findings highlight the potential clinical value of CT-derived anatomy in improving non-invasive assessment and prediction of portal hypertension

Registration and protocol

This systematic review was not prospectively registered and no review protocol was published.

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7 Appendix A

Scopus: 591 results TITLE-ABS-KEY(("splenic volume" OR "spleen volume" OR "splenic size" OR "spleen size" OR "liver volume" OR "hepatic volume" OR "liver size" OR "hepatic size" OR "liver-spleen ratio" OR "spleen-liver ratio" OR "hepatic-splenic ratio" OR (("splenic artery" OR "splenic arterial" OR "splenic arter*" OR "arteria lienalis") AND (diameter OR size OR caliber OR radius OR width)) OR (("splenic vein" OR "splenic venous" OR "vena lienalis") AND (diameter OR size OR caliber OR radius OR width)) OR (("portal vein" OR "portal venous" OR "vena portae") AND (diameter OR size OR caliber OR radius OR width)) OR (("hepatic artery" OR "hepatic arterial" OR "arteria hepatica") AND (diameter OR size OR caliber OR radius OR width)) OR (("superior mesenteric vein" OR "mesenteric vein" OR "superior mesenteric venous" OR "vena mesenterica superior") AND (diameter OR size OR caliber OR radius OR width)) OR "3D segmentation" OR "3D-segmentation" OR "CT volumetry" OR "CT-volumetry") AND ("portal pressure" OR"portal venous pressure" OR "hepatic venous pressure gradient" OR HVPG) AND ("liver cirrhosis" OR "cirrhosis" OR cirrhotic OR "portal hypertension" OR "portal hypertensive"))

PubMed: 281 results (("splenic volume"[tiab] OR "spleen volume"[tiab] OR "splenic size"[tiab] OR "spleen size"[tiab] OR "liver volume"[tiab] OR "hepatic volume"[tiab] OR "liver size"[tiab] OR "hepatic size"[tiab] OR "liver-spleen ratio"[tiab] OR "spleen-liver ratio"[tiab] OR "hepatic-splenic ratio"[tiab] OR (("splenic artery"[tiab] OR "splenic arterial"[tiab] OR "splenic arter*"[tiab] OR "arteria lienalis"[tiab]) AND (diameter[tiab] OR size[tiab] OR caliber[tiab] OR calibre[tiab] OR radius[tiab] OR width[tiab])) OR (("splenic vein"[tiab] OR "splenic venous"[tiab] OR "vena lienalis"[tiab]) AND (diameter[tiab] OR size[tiab] OR caliber[tiab] OR calibre[tiab] OR radius[tiab] OR width[tiab])) OR (("portal vein"[tiab] OR "portal venous"[tiab] OR "vena portae"[tiab]) AND (diameter[tiab] OR size[tiab] OR caliber[tiab] OR calibre[tiab] OR radius[tiab] OR width[tiab])) OR (("hepatic artery"[tiab] OR "hepatic arterial"[tiab] OR "arteria hepatica"[tiab]) AND (diameter[tiab] OR size[tiab] OR caliber[tiab] OR calibre[tiab] OR radius[tiab] OR width[tiab])) OR (("superior mesenteric vein"[tiab] OR "mesenteric vein"[tiab] OR "superior mesenteric venous"[tiab] OR "vena mesenterica superior"[tiab]) AND (diameter[tiab] OR size[tiab] OR caliber[tiab] OR calibre[tiab] OR radius[tiab] OR width[tiab])) OR "3D segmentation"[tiab] OR "3D-segmentation"[tiab] OR "CT volumetry"[tiab] OR "CT-volumetry"[tiab]) AND ("portal pressure"[tiab] OR "portal venous pressure"[tiab] OR "hepatic venous pressure gradient"[tiab] OR HVPG[tiab]) AND ("Liver Cirrhosis"[MeSH] OR "liver cirrhosis"[tiab] OR cirrhosis[tiab] OR cirrhotic[tiab] OR "Hypertension, Portal"[MeSH] OR "portal hypertension"[tiab] OR "portal hypertensive"[tiab]))

8 Appendix B

Table 5: Wordcount by chapter

Chapter	Title	Wordcount
1	Abstract	240
2	Introduction	328
3	Methods	872
4	Results	482
5	Discussion	604
6	Conclusion	143
Total		**2669 words**

F Research Proposal

The approved research proposal submitted at the start of this project is included in this appendix without modifications.

Een patiëntspecifiek model voor portale drukverlaging na Transjugulaire Intrahepatische Portosystemische Shunt (TIPS)

KTO-AS25011, Miltembolisatie-EMC, GR25018
Mila Den Hollander (6038395), Willem Grasso (5579090), Casper Bonte (5788013) en Bauke Scheerder (5564689)
Opleiding Klinische Technologie, Technische Universiteit Delft / Erasmus MC / LUMC
Begeleiders: dr. Kay Pieterman (interventieradioloog, Erasmus MC) en dr. Raoel Maan (MDL-arts, Erasmus MC)

1 Inleiding

Portale hypertensie is een klinisch probleem dat ontstaat door een verhoogde vaatweerstand in de levercirculatie, wat in de Westerse wereld in 90% van de gevallen wordt veroorzaakt door levercirrose.

Portale hypertensie is een verhoogde drukgradiënt tussen de poortader en de levervene (HVPG >5 mmHg). Vanaf een HVPG >10 mmHg is het drukverschil klinisch significant en stijgt het risico op ernstige complicaties zoals refractaire ascites, het hepatorenaal syndroom en levensbedreigende varicesbloedingen [1].

Bij het falen van medicamenteuze behandelingen is de standaardprocedure om een 'Transjugulaire Intrahepatische Portosystemische Shunt' (TIPS) te plaatsen. Bij deze ingreep wordt percutaan een bypass in de lever aangelegd om een deel van het bloed direct van de poortader naar de leverader (vena hepatica) te laten stromen.

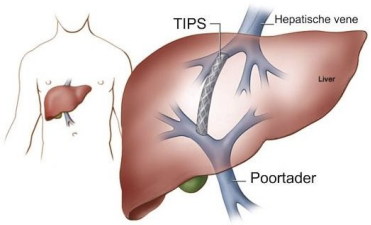

Figure 1: Transjugulaire Intrahepatische Portosystemische Shunt (TIPS)

Hoewel een behandeling met TIPS effectief is, brengt de ingreep aanzienlijke risico's met zich mee, zoals de operatieve belasting en een verhoogde kans op hepatische encefalopathie, wat gepaard gaat met verwardheid, sufheid en concentratieproblemen. [2] Voor artsen is het momenteel nog lastig om precies te kunnen voorspellen hoe de individuele hemodynamiek van een patiënt zal reageren. Om een goede afweging te kunnen maken tussen de drukverlaging en mogelijke complicaties, is de ontwikkeling van een model dat de hemodynamische respons vooraf kan voorspellen een goede aanvulling voor de arts in het maken van deze keuze.

Om hemodynamische veranderingen te voorspellen, leunen bestaande modellen [3] in de literatuur voornamelijk op complexe dynamische flow-metingen, zoals verkregen via Doppler-echografie of meer complexe radiomics-methoden. Het grote nadeel van deze flow-gebaseerde modellen is dat de benodigde metingen tijdrovend en patiëntbelastend zijn, en bovendien lang niet altijd standaard beschikbaar zijn in de klinische praktijk.

De portale druk wordt niet alleen bepaald door de leverweerstand, maar ook door de instroom van bloed vanuit de milt en de specifieke geometrie van het portale vaatbed. De portale druk en flow worden echter anatomisch weerspiegeld door de grootte van de organen en de dimensies van het portale vaatbed. Zo is in eerdere studies [4] aangetoond dat levervolume (verwant met intrahepatische weerstand) en miltvolume (verwant portale instroom) sterk gecorreleerd zijn met portale hemodynamiek en drukveranderingen. Door gebruik te maken van deze patiëntspecifieke anatomische parameters, kan de hemodynamische respons mogelijk nauwkeuriger worden ingeschat.

Dit onderzoek richt zich op de ontwikkeling van een predictiemodel dat de portale bloeddrukdaling na TIPS-plaatsing voorspelt. Dit model kunnen artsen gebruiken om een patiëntspecifieke inschatting te maken of TIPS een goede behandeloptie is, door vooraf mogelijk beter een inschatting te maken over de verwachte drukverlaging op basis van een CT-scan. Hiermee kan dit onderzoek bijdragen aan een patiëntspecifiekere behandeling bij portale hypertensie.

2 Onderzoeksvragen

2.1 KTO-A

Hoe worden anatomische parameters (miltvolume, levervolume, de diameter van de arteria en vena lienalis en de diameter van de vena porta en vena mesenterica superior) in de literatuur fysiologisch en wiskundig gerelateerd aan de portale druk en hemodynamiek?

2.2 KTO-B

Het doel van KTO-B is het ontwikkelen van een klinisch toepasbaar voorspellend model dat de portale drukverandering na TIPS voorspelt op basis van 3D-segmentatie van milt- en levervolume, de diameter van de arteria en vena lienalis, en de diameter van de vena portae en vena mesenterica superior.

Van de categorieën van het onderzoek van Zwart en de Vries, valt dit onderzoek binnen de categorie Model [5].

3 Verwachte aanpak

Het onderzoek bestaat uit twee delen. In de eerste fase wordt door middel van literatuuronderzoek de wiskundige relatie tussen anatomische parameters en portale druk(verandering) geïnventariseerd. Deze relaties worden gebruikt om een relevante modelarchitectuur en modelparameters te selecteren en om aannames over de vorm van het model te kunnen onderbouwen.

In de tweede fase wordt een patiëntcohort geanalyseerd waarbij patiënten zijn behandeld met TIPS. Van deze patiënten worden CT-scans gebruikt om de milt en lever te segmenteren met behulp van 3D Slicer in combinatie met automatische segmentatie software, waarna volumetrische parameters worden bepaald. Op basis van de 3D-segmentaties van het Erasmus MC TIPS cohort wordt een model opgesteld dat de verwachte portale drukverlaging na TIPS voorspelt.

Om dit model klinisch toepasbaar te maken, worden alleen parameters gebruikt die direct uit de CT-scan zijn afgeleid.

Het model wordt intern gevalideerd door k-fold cross-validatie met een trainingsset en een testset, waarbij de daadwerkelijk gemeten drukverandering wordt vergeleken met de modeloutput.

4 Benodigde faciliteiten

Voor het uitvoeren van dit onderzoek zijn de volgende materialen en faciliteiten nodig:

- Toegang tot CT-scans van een bestaand TIPS cohort van 360 patiënten met beschikbare portale drukmetingen voor en na TIPS (Via de opdrachtgevers, data uit Erasmus MC).
- Toestemming voor het gebruik van patiëntdata en bijbehorende ethische goedkeuring (via Erasmus MC).
- 3D Slicer, de software voor medische beeldanalyse, voor het segmenteren van de lever en milt, het bepalen van volumetrische parameters en het bepalen van de diameters van de betreffende vaten (te installeren op onze laptop en beschikbaar op computers in Erasmus MC). Hierbij wordt ook gebruikgemaakt van automatische segmentatiesoftware om tijd te besparen en interobservervariabiliteit te verkleinen.
- Python als statistische software voor dataverwerking en modellering (beschikbaar op onze laptop).

5 Beoogde einduitkomst

De beoogde einduitkomst van dit onderzoek is een werkend, patiëntspecifiek model waarmee de portale drukverlaging na plaatsing van een TIPS kan worden voorspeld op basis van 3D-gesegmenteerde volumes en diameters.

Het eindproduct bestaat uit een onderbouwd model, een dataset met berekende en gemeten drukveranderingen en een analyse van de modeluitkomsten in relatie tot klinische data. Dit model kan als hulpmiddel gebruikt worden door artsen bij het afwegen of deze behandeling passend is voor een specifieke patiënt.

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G Research Plan

The approved research plan submitted for this project is included in this appendix without modifications.

Een patiëntspecifiek machine learning model voor portale drukverlaging na Transjugulaire Intrahepatische Portosystemische Shunt (TIPS)

KTO-AS25011, Miltembolisatie-EMC, GR25018
Mila Den Hollander (6038395), Willem Grasso (5579090), Casper Bonte (5788013) en Bauke Scheerder (5564689)
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1 Inleiding

Portale hypertensie is een klinisch probleem dat ontstaat door een verhoogde vaatweerstand in de levercirculatie, met als hoofdoorzaak levercirrose. Bij portale hypertensie is er sprake van een verhoogde drukgradiënt (HVPG >5 mmHg), wat vanaf >10 mmHg leidt tot ernstige complicaties zoals refractaire ascites, hepatorenaal syndroom en varicesbloedingen [1].

Bij het falen van medicamenteuze behandelingen is de standaardprocedure om een 'Transjugulaire Intrahepatische Portosystemische Shunt' (TIPS) te plaatsen. Bij deze ingreep wordt percutaan een bypass in de lever aangelegd om een deel van het bloed direct van de poortader naar de leverader (vena hepatica) te laten stromen.

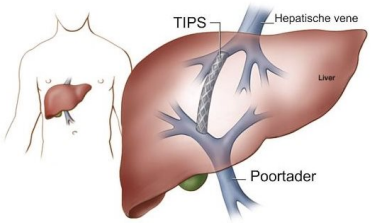

Figure 1: Transjugulaire Intrahepatische Portosystemische Shunt (TIPS)

Hoewel een behandeling met TIPS effectief is, brengt de ingreep aanzienlijke risico's met zich mee, waarvan hepatische encefalopathie de belangrijkste complicatie is. Deze complicatie geeft verwardheid, sufheid en concentratieproblemen en heeft veel invloed op de kwaliteit van leven van de patiënten. [2]

Er is daarbij toenemende interesse in alternatieve behandelopties, zoals miltembolisatie, waarbij de bloedtoevoer naar de milt wordt verminderd om de portale instroom en daarmee de portale druk te verlagen. Hoewel deze techniek potentieel minder invasief is, is er nog beperkte kennis over de te verwachten drukverandering en klinische effectiviteit in vergelijking met TIPS. Voor artsen is het momenteel nog lastig om precies te kunnen voorspellen hoe de individuele hemodynamiek van een patiënt zal reageren op TIPS. Om een goede afweging te kunnen maken tussen de drukverlaging en mogelijke complicaties, is de ontwikkeling van een model dat de hemodynamische respons vooraf kan voorspellen een goede aanvulling voor de arts in het maken van deze keuze.

Om hemodynamische veranderingen te voorspellen, leunen bestaande modellen [3] in de literatuur voornamelijk op complexe dynamische flow-metingen, zoals verkregen via Doppler-echografie of meer complexe radiomics-methoden. Het grote nadeel van deze flow-gebaseerde modellen is dat de benodigde metingen tijdrovend en patiëntbelastend zijn, en bovendien lang niet altijd standaard beschikbaar zijn in de klinische praktijk. De portale druk wordt niet alleen bepaald door de leverweerstand, maar ook door de instroom van bloed vanuit de milt en de specifieke geometrie van het portale vaatbed. De portale druk en flow worden echter anatomisch weerspiegeld door de grootte van de organen en de dimensies van het portale vaatbed. Zo is in eerdere studies [4] aangetoond dat levervolume (verwant aan intrahepatische weerstand) en miltvolume (verwant aan portale instroom) sterk gecorreleerd zijn met portale hemodynamiek en drukveranderingen. Door gebruik te maken van deze patiëntspecifieke anatomische parameters, kan de hemodynamische respons mogelijk nauwkeuriger worden ingeschat.

Dit onderzoek richt zich op de ontwikkeling van een anatomisch predictiemodel dat de portale bloeddrukdaling na TIPS-plaatsing voorspelt. Dit model kunnen artsen gebruiken om een patiëntspecifieke inschatting te maken of TIPS een goede behandeloptie is, door vooraf mogelijk beter een inschatting te maken over de verwachte drukverlaging op basis van een CT-scan.

Ook kan dit model in de toekomst gebruikt worden om de verwachte effecten van TIPS te vergelijken met alternatieve behandelopties zoals miltembolisatie, en zo bijdragen aan een beter onderbouwde keuze tussen verschillende behandelstrategieën.

Hiermee kan dit onderzoek bijdragen aan een meer patiëntspecifieke behandeling bij portale hypertensie.

2 Onderzoeksvragen en hypothesen

2.1 KTO-A

Uit onze literatuurstudie is gebleken dat de diameter van de vena portae, vena lienalis en de vena mesenterica superior, de volumes van de milt en lever en de milt/lever ratio gecorreleerd zijn aan de portale druk(verandering). Meestal wordt dit lineair beschreven, maar in meerdere studies ook niet-lineair. Omdat voor ons nog onduidelijk is of de variabelen lineair of niet-lineair zullen correleren, ontwikkelen wij twee modellen. Een verklaarbaar lineair regressiemodel en een tree-based XGBoost (eXtreme Gradient Boosting) model.

2.2 KTO-B

Het doel van KTO-B is het ontwikkelen van een klinisch toepasbaar patiëntspecifiek predictiemodel wat de portale drukverlaging na TIPS-plaatsing voorspelt op basis van CT-afgeleide anatomische parameters. Om dit model klinisch toepasbaar te maken, wordt het ontwikkeld met uitsluitend parameters (gebaseerd op KTO-A) die direct en routinematig uit standaard CT-scans kunnen worden verkregen. Het predictiemodel zal worden geïntegreerd in een prototype (web)applicatie om het model eenvoudig te kunnen gebruiken in de klinische praktijk. Door te streven naar een interpreteerbaar model, biedt het artsen beter inzicht om individuele behandelkeuzes te kunnen overwegen. In de toekomst kan dit model bovendien helpen om TIPS af te wegen tegen alternatieven zoals miltembolisatie.

Hypothese: Wij verwachten dat anatomische parameters gecombineerd kunnen worden in een predictiemodel voor het voorspellen van de portale drukverandering na TIPS. Hoewel dit model waarschijnlijk minder accuraat is dan bestaande complexe, flow-gebaseerde modellen, verwachten wij dat het door het gebruik van eenvoudig verkrijgbare CT-parameters wel geschikt is voor het maken van een klinische schatting van de behandeluitkomst.

3 Verwachte aanpak

3.1 Parameters

Op basis van de resultaten van KTO-A worden alle anatomische parameters die in de literatuur een significante relatie tonen met de druk(verandering) én verkrijgbaar zijn uit een CT-scan, geïncludeerd in de initiële modelvorming. Deze parameters worden gemeten op de beschikbare CT-scans van het TIPS-cohort. Tijdens het trainen van de modellen worden variabelen die niet significant bijdragen aan de voorspelkracht weggefilterd of in weging geminimaliseerd. Dit vermindert overfitting en draagt bij aan de klinische interpreteerbaarheid.

3.2 Cohort

Voor dit retrospectieve onderzoek wordt gebruikgemaakt van een bestaand Erasmus MC TIPS-cohort van circa 360 patiënten met beschikbare portale drukmetingen vóór en na TIPS-plaatsing. De gebruikte patiëntdata zijn afkomstig uit een bestaand cohort waarvoor reeds METC-goedkeuringen zijn verkregen via Erasmus MC. Het bijbehorende METC-nummer is gevraagd en zal in het eindrapport vermeld worden. Inclusiecriteria zijn de beschikbaarheid van geschikte CT-scans voorafgaand aan TIPS en complete drukmetingen. Patiënten met incomplete beeldvorming of onvoldoende beeldkwaliteit worden geëxcludeerd. Voor de analyse worden contrastversterkte CT-scans gebruikt uit de portoveneuze fase, omdat hierin de portale venen en abdominale organen optimaal zichtbaar zijn voor segmentatie en diameterbepaling.

3.3 Segmentatie

De CT-scans worden geanalyseerd met 3D Slicer en TotalSegmentator. De segmentaties van de lever, milt, vena porta en vena lienalis worden semiautomatisch uitgevoerd door de onderzoekers met behulp van de verschillende softwarepaketten. Om de betrouwbaarheid van de segmentaties te waarborgen, worden alle segmentaties gecontroleerd door meerdere onderzoekers en vergeleken op consistentie. Bij grote onderlinge verschillen vindt gezamenlijke herbeoordeling plaats. De arteria lienalis, vena mesenterica superior en arteria hepatica worden handmatig gesegmenteerd op gestandaardiseerde anatomische locaties op axiale of multiplanaire reconstructies van de CT-scans, op basis van een gestandaardiseerde meetmethode opgesteld in overleg met de begeleiders. Daarnaast wordt de aanwezigheid en ernst van ascites meegenomen als klinische variabele, gebaseerd op de drainagegeschiedenis van de patiënt.

3.4 Modelvorming

Op basis van de verkregen anatomische parameters uit KTO-A wordt een predictiemodel ontwikkeld voor het voorspellen van de portale druk (PPG) na een TIPS-procedure, op basis van de HVPG, anatomische groottes en enkele klinische variabelen vooraf aan de TIPS-procedure.

3.4.1 Data Preprocessing

Voordat het model getraind kan worden, ondergaat de data een standaard preprocessing pipeline. Bij missende data wordt eerst gekeken of de segmentatiesoftware een variabele is vergeten, zodat die alsnog gemeten

kan worden. Als andere data ontbreekt wordt de patiënt geëxcludeerd. Daarna worden alle variabelen gestandaardiseerd via Z-score normalisatie. Categorische variabelen (zoals Child-Pugh score of de aanwezigheid van ascites/varices) worden middels One-Hot Encoding omgezet naar binaire waarden.

3.4.2 Modelarchitectuur en feature selectie

Tijdens de modelontwikkeling wordt onderzocht welke parameters daadwerkelijk bijdragen aan de voorspellende waarde van het model. Om het model te vereenvoudigen en overfitting te verminderen, worden parameters die geen significante bijdrage leveren of sterke multicollineariteit veroorzaken naar nul gedwongen of geëxcludeerd. In het lineaire regressie wordt dit gedaan door de elasticnet regularisatie, wat een combinatie is van L1- en L2 regularisatie. De L1-regularisatie (LASSO) dwingt de coëfficiënten van irrelevante variabelen naar exact nul, wat fungeert als feature-selectie. De L2-regularisatie (Ridge) zorgt tegelijkertijd voor wiskundige stabiliteit wanneer inputvariabelen sterke multicollineariteit vertonen. Als tweede model wordt een XGBoost model gemaakt. Dit tree-based algoritme leert sequentieel via gradient descent, waarmee het complexe niet-lineaire verbanden kan trekken. Een bijkomend voordeel is dat XGBoost intrinsiek L1- en L2-regularisatie toepast tijdens de modelopbouw, wat irrelevante variabelen afstraft en resulteert in een lage feature importance.

Het model wordt opgebouwd in Python met bibliotheken zoals Scikit-learn en XGBoost. Het model wordt getraind in de online omgeving Kaggle.

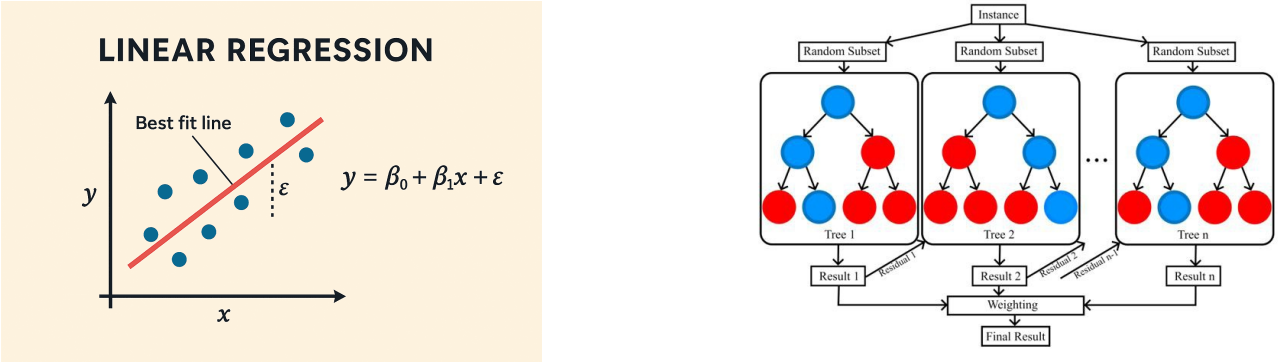

Figure 2: Links: Lineaire regressie model. Rechts: XGBoost model.

3.4.3 Model validatie en evaluatie

Het predictiemodel wordt intern gevalideerd met behulp van 5x5 Nested Cross-Validation. Hierbij wordt de data twee keer opgesplitst in een binnenste lus voor hyperparameter tuning en een buitenste lus voor interne validatie van de modelprestaties. De prestaties van het model worden geëvalueerd met behulp van de Mean Absolute Error(MAE), de Root Mean Squared Error (RMSE) en de determinatiecoëfficient (R^2). De MAE is de meest klinisch relevante maatstaf voor de behandelend arts. Wij denken dat het model klinisch relevant is als het model een MAE behaalt van <3 mmHg.

3.4.4 Hyperparameter tuning

Het optimaliseren van de hyperparameters is belangrijk om de prestaties en generaliseerbaarheid van het model te verbeteren. Hyperparameters zijn configuratie-instellingen van het algoritme die niet direct uit de data kunnen worden afgeleid. Voor de twee modelarchitecturen worden de volgende parameters geoptimaliseerd:

- Lineaire Elastic Net regressie: de primaire focus ligt op twee parameters: de regularisatieparameter lambda, die de mate van feature-selectie bepaalt, en de L1_Ratio, die een balans zoekt tussen L1 en L2 regularisatie. Omdat dit een eenvoudig wiskundig model is met slechts twee hyperparameters, voldoet een grid search en is dit computationeel efficiënt te berekenen.
- XGBoost: XGBoost is van nature zeer gevoelig voor overfitting, zeker bij een relatief kleine dataset (N=360). Hierbij worden de parameters getuned die de complexiteit van de beslisbomen reguleren om overfitting te voorkomen. Dit zijn de learning_rate, min_samples_per_leaf, N_estimators, Max_depth en subsample. Voor dit model is een traditionele grid search computationeel onhaalbaar, omdat de benodigde rekentijd exponentieel toeneemt per toegevoegde hyperparameter. Daarom wordt voor dit model Bayesiaanse optimalisatie gebruikt, geïmplementeerd via de Python-bibliotheek Optuna. Optuna bouwt een probabilistisch surrogaatmodel van de hyperparameter-ruimte. Het algoritme leert van eerdere iteraties en kan hiermee relatief snel convergeren naar de optimale hyperparameter combinaties.

3.4.5 Uiteindelijke modelselectie

Na het trainen van beide modellen worden de modelprestaties met elkaar vergeleken. Het uiteindelijke model wordt geselecteerd op basis van interpreteerbaarheid en validiteit.

3.5 Applicatieontwikkeling

Het eindproduct van dit onderzoek zal een klinisch toepasbare applicatie zijn waarin artsen de relevante anatomische parameters kunnen invoeren. Op basis van het geïntegreerde predictiemodel genereert de applicatie vervolgens een voorspelling van de verwachte portale drukverandering na TIPS. Hiermee biedt de applicatie een moderne en toegankelijke manier om artsen te ondersteunen bij patiëntspecifieke behandelkeuzes. Hoewel vooraf nog segmentatie van de CT-scans nodig blijft om de anatomische parameters te verkrijgen, zal de uiteindelijke voorspelling volledig gebaseerd zijn op het door ons ontwikkelde model.

4 Benodigde faciliteiten

Voor het uitvoeren van dit onderzoek zijn de volgende materialen en faciliteiten nodig:

- Toegang tot CT-scans van een bestaand TIPS cohort van 360 patiënten met beschikbare portale drukmetingen voor en na TIPS (Via de opdrachtgevers, data uit Erasmus MC).
- Toestemming voor het gebruik van patiëntdata en bijbehorende ethische goedkeuring (verkregen via Erasmus MC).
- 3D Slicer, de software voor medische beeldanalyse (te installeren op onze laptop en beschikbaar op computers in Erasmus MC). En TotalSegmentator, de automatische segmentatiesoftware (online beschikbaar via onze begeleiders)
- Python als statistische software voor dataverwerking en modellering (beschikbaar op onze laptop).
- Harde schijf voor het opslaan van de CT-beelden en segmentatiebestanden (in ons bezit).

5 Cruciale momenten en potentiële knelpunten

- **Segmentatie van CT-scans:** Het segmenteren van alle CT-scans kan tijdsintensief zijn en gevoelig voor fouten of interobservervariatie. *Mitigatie:* gebruik van semiautomatische segmentatie en het opstellen van een gestandaardiseerd segmentatieprotocol. Indien nodig worden steekproefsgewijs segmentaties gecontroleerd door meerdere onderzoekers.
- **Datacompleetheid:** Patiëntdossiers kunnen incomplete gegevens bevatten, zoals ontbrekende drukmetingen of CT-scans van onvoldoende kwaliteit. *Mitigatie:* vooraf definiëren van inclusie- en exclusiecriteria en werken met een voldoende groot cohort om uitval op te vangen.
- **Variatie in parameteracquisitie:** Verschillen in parameteracquisitie kunnen invloed hebben op de nauwkeurigheid van metingen en daardoor op de nauwkeurigheid van het model, zoals het verschil in drukmeting voor TIPS (HVPG) en na TIPS (PPG). *Mitigatie:* standaardiseren van meetmethoden.
- **Rekentijd en modeltraining:** Het uitvoeren van de data-analyse en modelontwikkeling kan veel rekentijd vergen, vooral bij grote datasets en complexe modellen. *Mitigatie:* efficiënte modelarchitectuur opstellen, testen van code op kleinere subsets van de data en indien nodig gebruikmaken van computers met voldoende rekenkracht binnen het Erasmus MC.
- **Modeloverfitting:** Door het includeren van veel parameters bestaat het risico dat het model overfit raakt op de trainingsdata. Daarnaast is specifiek het XGBoost model zeer gevoelig voor overfitting. *Mitigatie:* toepassen van cross-validatie en variabelenselectie d.m.v. de ingebouwde modelarchitectuur en zorgvuldige hyperparameter tuning.
- **Beperkte voorspellende waarde van anatomische parameters:** Het is mogelijk dat anatomische parameters alleen onvoldoende zijn om portale drukverandering nauwkeurig te voorspellen. *Mitigatie:* kritische evaluatie van modelprestaties en duidelijke rapportage van beperkingen.

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H Individual Contributions

Casper Bonte

Projectaanpak: Ik ben blij dat we na de eerste week zijn verandert van miltembolisatie naar een TIPS cohort. Het leek de eerste week heel erg dat we ons door allemaal vreemde bochten moesten wringen om iets van een logische onderzoeksopzet te kunnen krijgen omdat er bijna geen data van beschikbaar was.

Primaire rol: Ik heb mij vooral bezig gehouden met het model zelf. Ik heb de modelarchitectuur verzonnen en de code van de modellen geschreven. Doordat ik een minor had gevolgd over machine learning en AI, had ik al de benodigde achtergrondkennis om hier aan te kunnnen werken.

Evenredige bijdrage: Naar mijn idee hebben alle teamleden ongeveer een evenredige bijdrage geleverd. We hebben wel allemaal net andere rollen gehad. Ik heb wat meer gefocused op de modellen, willem heeft de app gemaakt, mila had goed overzicht en heeft veel aan het verslag gewerkt ect. We hebben hierin geen duidelijke verdeling gemaakt, maar iedereen heeft op een organische wijze gewerkt aan de onderdelen die zij leuk vonden / goed in waren.

Groepswerk en groepssamenstelling: Tijdens de week waarin de groepjes werden gevormd lag ik op de intensive care, dus was ik niet zo bezig met het vormen van een groepje. Op de laatste dag van de inschrijvingen kon ik mij gelukkig aansluiten bij dit groepje. Ik denk dat we in dit groepje allemaal verschillende kwaliteiten hadden waarbij we elkaar goed hebben aangevuld. Ik ben bijvoorbeeld zelf niet heel goed in het plannen, maar daar was een andere groepsgenoot veel mee bezig, waardoor we elkaar dus goed hebben aangevuld. Uiteindelijk vond ik het een prettige samenwerking waarbij ik denk dat we een mooi resultaat hebben kunnen neerzetten.

Aan het begin van het project zou ik duidelijker verwachtingen hadden willen uitspreken over wanneer er aan het project gewerkt wordt. Werk je door tijdens de lunch? Gaan we naar huis? Werk je door in het weekend? Ik had zelf bijna nooit tijd in het weekend, waardoor ik graag doordeweeks veel af wilde maken. Soms merkte ik dat andere groepsgenoten s'ochtens later aankwamen of s'middags eerder weggingen en dan dit afmaakten in het weekend.

Mila den Hollander Omdat het op het begin van KTO-A nog niet duidelijk was welke data we zouden hebben en wat voor onderzoek we gingen doen, was het een redelijk rommelige start. Ik ben blij dat we dat snel hebben opgepakt en snel de keuze hebben gemaakt om onze oorspronkelijke opdracht te veranderen. Hierna hebben we de grote lijnen van ons onderzoeksplan aangehouden, maar omdat we steeds meer ontdekten konden we tijdens KTO-A al, maar ook nog tijdens KTO-B, kleine aanpassingen doen waar nodig. Zo hebben we uiteindelijk een heldere en duidelijke onderzoeksuitvoer kunnen doen.

Naar mijn idee ben ik veel bezig geweest met de planning en het overzicht bewaren. Zo hebben we duidelijke deadlines voor onszelf gesteld en konden we gestructureerd werken. Ik heb ook vaak kritisch naar het project gekeken en heb ik veel aanpassingen kunnen voorstellen. Concreet ben ik ook veel bezig geweest met de manier van segmenteren en hoe we dit optimaal konden doen. We hebben tijdens het project niet duidelijke rollen verdeeld, maar bepaalde taken pakten mensen automatisch zelf op. Dit was fijn omdat we hierdoor niet continu bezig hoefden te zijn met of iedereen wel iets deed, en daardoor had iedereen ongeveer een evenredige bijdrage.

Wat ik heb geleerd van het als groep werken aan dit project, is dat het heel nuttig is om aandacht te besteden aan de planning en aan het overzocht behouden. Door aan het begin duidelijk te hebben wanneer we bepaalde dingen af willen hebben, zit iedereen de rest van het project op één lijn. Hierdoor is het ook veel makkelijker om bepaalde dingen te vragen van groepsgenoten, omdat je kleine dingen kan vragen van iemand als de deadline er bijna is. Ook door bijvoorbeeld een ander document met daarin de structuur te maken voor het rapport, waar in iedereen kan afstrepen wat al verwoord is, kan zorgen dat we veel efficiënter werken.

Wat ik volgende keer anders zou doen is dat we bepaalde dingen vroegtijdiger uitzoeken. Onze planning liep bijvoorbeeld heel anders doordat we er later achterkwamen dat de data ophalen veel langer duurde dan we hadden gedacht. Ook hadden we uiteindelijk een stuk minder data beschikbaar waardoor de kwaliteit van ons onderzoek ook anders uitpakte. Dit zijn dingen waar we in eerste instantie een aanname over hebben gemaakt, maar waar ik volgende keer op het begin al kritisch over na zou denken.

Ik denk dat we een goede groepssamenstelling hadden. We hadden allemaal andere kwaliteiten die goed van pas kwamen, terwijl we in grote lijnen op één lijn lagen. Ook konden we goed samen discussiëren

en kritisch nadenken over alle, ook kleine, keuzes die in ons onderzoek gemaakt konden worden.

Bauke

Ik vond dat het in het begin niet heel goed ging omdat we als groepje wat dingen over het hoofd hadden gezien, of niet kritisch genoeg waren naar onze opdrachtgevers. (oa. of de initiele opdracht mogelijk was met de data beschikbaar) en de deadlines niet overzichtelijk hadden waardoor we een beetje achter de feiten aanliepen. Daarna hebben we dit heel goed opgepakt en structuur aangebracht in onze werkwijze. Mijn primaire rol binnen het groepje was oa. het kritsch nadenken over bepaalde onderwerpen die soms over het hoofd werden gezien. En ook overzicht houden over het project. Verder ben ik veel bezig geweest met het downloaden van CT's, het segmenteren en het schrijven van het report. Naar mijn idee hebben alle teamgenoten ongeveer evenredig bijgedragen aan het project. Iedereen heeft zijn eigen rol aangenomen in waarin iedereen goed is, wat denk ik tot een goede samenwerking heeft geleid. Dat Als je met een groep werkt juist moet waken voor dat je dingen niet over het hoofd ziet. Je kunt niet uitgaan dat groepsgenoten bepaalde dingen wel zien of rekening meehouden. Iedereen moet kritisch blijven nadenken.

Wat ik de volgende keer anders zou doen is een betere comminucatie over wanneer aan het project gewerkt zou worden. Hier ben ik zelf ook schuldig aan.

Vanaf het begin een planning maken, dit hebben we echter wel goed opgepakt.

Ik denk dat onze groepssamenstelling goed was, iedereen heeft de ambitie om er echt iets van te maken. Verder zijn we allen flexibel met samenwerken en taken verdelen, waardoor we goed samen konden werken, maar ook los van elkaar, elkaar goed konden aanvullen.

Willem

Tijdens dit project lag mijn grootste rol bij het ontwikkelen en werkend maken van de applicatie. Casper heeft vooral aan de modelcode gewerkt. Op basis van die output heb ik de functionele code van de app gemaakt en dit omgezet naar een werkende applicatie. Ik heb er ook voor gezorgd dat de app op mijn telefoon kon draaien en heb getest of de invoerwaarden, de modeloutput en de weergave in de app goed werkten.

Daarnaast heb ik meegewerkt aan de CT-metingen en segmentatie. Deze taken waren eerlijk verdeeld over de vier groepsleden, waardoor ik ongeveer een kwart van alle CT-scans heb gemeten. Ook heb ik geholpen met het downloaden van de CT-data. Verder heb ik bijgedragen aan het schrijven van het verslag, vooral door fouten te verbeteren, onderdelen aan te vullen, de stukken over de applicatie te schrijven en te controleren of bepaalde claims goed genoeg door bronnen werden ondersteund.

Ik vond de projectaanpak goed. Wat minder goed ging, was dat de dataset vanuit de begeleiders achteraf veel incompleter bleek dan verwacht.

Naar mijn idee hebben alle groepsleden ongeveer evenredig bijgedragen aan het eindresultaat. Sommige groepsleden hebben wat meer gedaan binnen de onderdelen waar zij sterker in waren, maar dat hielp juist om het proces sneller vooruit te krijgen. De gezamenlijke taken, zoals CT-metingen, segmentatie, overleg met begeleiders en het downloaden van CT-scans, zijn eerlijk verdeeld.

Van dit project heb ik geleerd dat planning en duidelijke communicatie erg belangrijk zijn, zeker bij een project waarin zoveel verschillende onderdelen samenkomen. Ik merk ook dat ik beter ben geworden in proactief communiceren en eerder input geven tijdens het proces. Een volgende keer zou ik eerder uitzoeken welke data precies beschikbaar zijn en hoe compleet die data zijn, zodat onnodig werk zoveel mogelijk voorkomen kan worden.

Over het algemeen vond ik de groepssamenstelling erg goed. Ik kende Mila al goed, wat de communicatie makkelijk maakte, en Casper en Bauke waren ook een sterke toevoeging aan de groep. Iedereen had andere sterke punten, waardoor we het werk op een praktische manier konden verdelen.

I Meeting Minutes

The meeting minutes included in this appendix are presented in Dutch, as all meetings with the supervisors were conducted in Dutch. They have been included in their original language to preserve the accuracy and context of the discussions.

Bespreking eerste kennismaking met begeleiders

Besproken onderwerpen

- Introductie van de onderzoeksopdracht en de beschikbare faciliteiten.
- Toelichting op de huidige kennis rondom splenic artery embolisation (SAE) bij portale hypertensie.
- Beschikbaarheid van een groot retrospectief TIPS-cohort met CT-scans en portale drukmetingen vóór en na TIPS.
- Mogelijkheden voor segmentatie van CT-scans met 3D Slicer.
- Opzet van het literatuuronderzoek en het onderzoeksproject.

Conclusies

- Er is beperkte literatuur beschikbaar over het effect van SAE op de portale druk; bestaande studies bevatten kleine patiëntcohorten.
- Binnen het Erasmus MC is een groot cohort TIPS-patiënten beschikbaar met CT-scans en drukmetingen vóór en na TIPS.
- Het oorspronkelijke idee was om op basis van CT-afgeleide miltvolumes en literatuurgegevens te modelleren welke drukverlaging bereikt zou kunnen worden met SAE en dit te vergelijken met de gerealiseerde drukverlaging na TIPS.
- Voor het literatuuronderzoek dient niet alleen de drukverlaging, maar ook de complicaties en klinische uitkomsten van TIPS en SAE te worden meegenomen.
- De CT-scans kunnen worden geanalyseerd met 3D Slicer en segmentatiesoftware voor volumebepalingen van lever en milt.
- Er wordt een WhatsApp-groep aangemaakt voor laagdrempelig contact gedurende het project.

Bespreking aanpassing onderzoeksplan

Besproken onderwerpen

- Mogelijkheden voor validatie van het ontwikkelde model.
- Beschikbaarheid van gegevens van patiënten die een splenic artery embolisation hebben ondergaan.

Conclusies

- Er zijn geen datasets beschikbaar met portale drukmetingen vóór en na miltembolisatie.
- Wel zijn uitgebreide gegevens beschikbaar van patiënten behandeld met TIPS, inclusief CT-scans en drukmetingen.
- Besloten is daarom het onderzoek te richten op een predictiemodel voor de drukverandering na TIPS op basis van CT-afgeleide anatomische parameters en relevante variabelen uit de literatuur.

Bespreking onderzoeksplan en modelontwikkeling

Besproken onderwerpen

- Ontwikkeling van een eenvoudig anatomisch predictiemodel voor TIPS.
- Relevante anatomische parameters.

Conclusies

- Een eenvoudig CT-gebaseerd model heeft mogelijk klinische meerwaarde naast bestaande complexe hemodynamische modellen.

- Geadviseerd werd ook de diameter van de arteria hepatica mee te nemen als mogelijke voorspeller, vanwege de mogelijke relatie met ischemische complicaties na TIPS.
- De begeleiders adviseerden de theoretische onderbouwing hiervan uit de literatuur te onderzoeken.

Bespreking klinische eisen aan het model

Besproken onderwerpen

- Klinische toepasbaarheid van het predictiemodel.

Conclusies

- Het model dient de drukverandering na TIPS te voorspellen.
- Een gemiddelde fout groter dan circa 2 mmHg wordt klinisch onwenselijk geacht; een fout van ongeveer 1 mmHg heeft de voorkeur.
- Zowel anatomische als klinische variabelen kunnen gevonden worden en mogen in het model worden opgenomen.

Bespreking dataverzameling

Besproken onderwerpen

- Beschikbaarheid van patiëntgegevens en opslag van CT-scans.

Conclusies

- Tijdig starten met het verzamelen van de data is belangrijk vanwege de omvang van het cohort.
- Er is een externe harde schijf beschikbaar voor opslag van de CT-scans.
- Naast CT-scans zijn ook klinische gegevens beschikbaar, waaronder BMI, Child-Pugh-score en laboratoriumwaarden.

Bespreking ethiek en uitvoering segmentatie

Besproken onderwerpen

- Software en uitvoering van de segmentaties.
- Ethische goedkeuringen.

Conclusies

- De CT-scans zijn vervaardigd in de portoveneuze contrastfase.
- Horos en automatische segmentatiesoftware kunnen worden gebruikt voor lever- en miltsegmentatie.
- Per patiënt is de gebruikte stentdiameter beschikbaar in het procedureverslag.
- De geselecteerde patiënten maken deel uit van eerdere studies waarvoor METC-toestemming is verkregen.
- Voor toegang tot de data wordt een gastvrijheidsovereenkomst geregeld.
- Voor de bepaling van vaatdiameters wordt geadviseerd loodrecht op het vat te meten in coronale reconstructies op de locatie met de grootste diameter.
- Alle drukmetingen zijn verricht rondom de TIPS-procedure (direct vóór en direct na plaatsing).

Bespreking segmentatieprotocol

Besproken onderwerpen

- Feedback op meetprotocol vaatdiameters.
- Gestandaardiseerde meetmethode voor vaatdiameters op CT-scans.

Conclusies

- Aanbevolen werd om alleen CT-scans te includeren waarbij maximaal 12 maanden tussen CT en TIPS zat.
- Er werd gevraagd rekening te houden met aftakkingen van de arteria lienalis (zoals arteriae pancreaticae) tijdens de segmentatie.
- Het segmentatieprotocol werd verder geschikt bevonden.

Bespreking klinische relevantie van het model

Besproken onderwerpen

- Mogelijke toepassing van het model in de klinische praktijk.

Conclusies

- Het model kan artsen ondersteunen bij de beslissing om wel of geen TIPS te plaatsen.
- Een voorspelling van de post-TIPS portale druk kan helpen om het verwachte effect en het risico op hepatische encefalopathie beter af te wegen.
- Het model kan mogelijk gebruikt worden bij de keuze van de uiteindelijke stentdiameter.
- De huidige besluitvorming is grotendeels gebaseerd op de klinische toestand van de patiënt; een predictiemodel kan deze besluitvorming objectiever ondersteunen.
- De exacte benodigde drukverlaging voor een optimaal klinisch resultaat is nog niet volledig bekend.

+

J AI Statement

Claude Code was used to support the development of the visual layout and non-functional frontend components of the application. This included aspects such as colours, themes, spacing and general screen layout. These components were used to improve the presentation and usability of the application, but did not influence the statistical model, the input variables, the model coefficients or the final prediction output.

prompt 1: "I have only the brain of a medical app: the functional TypeScript code that does the math, with no screens yet. It estimates portal venous pressure (PVP) from patient data. There are three files: fields.ts lists all the inputs (12 measurements, plus 5 calculated ratios); predict.ts is a simple linear model that adds up each value times its weight to get a PVP number and a risk label; and xgb.ts is a XGBoost model that runs the inputs through decision trees. Both give back the same kind of result. Please build a real mobile app around this code using Expo with React Native. Make input screens for the fields, a switch to pick which model to use, and a result screen showing the predicted PVP, the risk category, and which inputs mattered most. Set it up so I can scan a QR code and test it right away on my phone with the Expo Go app. Don't change the functional code, just build the screens on top of it."

prompt 2: "Submit the app to my testflight account"

K Processed and Analysed Data

Table 3: Baseline cohort characteristics and anatomical parameters ($n = 144$)

Parameter	Mean ± SD or n	Available (%)
Demographics & Clinical		
BMI [kg/m^2]	26.1 ± 5.1	84.0
Liver Cirrhosis [n, %]	144	100.0
Refractory Ascites [n, %]	109	100.0
Esophageal Varices [n, %]	74	100.0
Anatomical Volumes		
Liver Volume [ml]	1780.4 ± 472.2	100.0
Spleen Volume [ml]	693.8 ± 395.0	100.0
Vascular Diameters		
Portal Vein [mm]	9.4 ± 0.9	100.0
Splenic Vein [mm]	9.9 ± 2.6	99.3
Superior Mesenteric Vein [mm]	9.0 ± 1.4	98.6
Splenic Artery [mm]	4.6 ± 1.2	89.6
Proper Hepatic Artery [mm]	5.7 ± 3.3	93.1
Left Renal Vein [mm]	8.6 ± 1.4	99.3
Ratios		
Spleen/Liver ratio [-]	0.37 ± 0.21	100.0
Spleen/BMI [ml/(kg/m^2)]	24.2 ± 11.9	84.0
Liver/BMI [ml/(kg/m^2)]	68.9 ± 21.5	84.0
SMV/Splenic Vein ratio [-]	1.4 ± 0.4	97.9
Portal Vein/Splenic Vein ratio [-]	1.6 ± 0.4	97.9
Hemodynamics & Intervention		
PPG pre [mmHg]	16.1 ± 5.3	100.0
PPG post [mmHg]	5.7 ± 2.9	100.0
Stent Diameter (post-PTA) [mm]	8=33(n), 9=7(n), 10=91(n)	91.7

L Source Code

Code and model architecture are mostly based on lectures and projects from the TU Delft minor 'Engineering with AI' in the courses 'Machine learning and introduction to AI' (TI3145TU), 'Deep learning' (TI3155TU) and 'Intermediate python programming' (TI3105TU).

Code of linear model:

```
#importeren van de benodigde libraries
import numpy as np
import pandas as pd
import optuna
from sklearn.metrics import mean_absolute_error
from sklearn.preprocessing import StandardScaler
from sklearn.pipeline import Pipeline
from sklearn.model_selection import KFold, cross_val_score
from sklearn.linear_model import ElasticNet
from sklearn.impute import KNNImputer
from sklearn.metrics import mean_absolute_error, mean_squared_error, r2_score

data = pd.read_csv(r"dataset_cohort.csv", sep = ';')
data.head()

#definieren van de features
features2 = [col for col in data.columns if col not in ['PatientID', target1]]
```

```
target2 = target1

#Training model
#definieren van de features
features_data_2 = data[features2]
target_data_2 = data[target2]
X = features_data_2.values
y = target_data_2.values
print("Pipeline 2")

#outer loop van cross validatie definieren, we gebruiken een random_state zodat de resultaten reprod
outer_cv = KFold(n_splits=5, shuffle=True, random_state=1)

# Lijst om de MAE van elke outer fold in op te slaan
outer_mae_scores = []

#Optuna log uit want er komt allemaal troep uit
optuna.logging.set_verbosity(optuna.logging.WARNING)

#objective functie
def objective(trial, X_train, y_train):
    alpha = trial.suggest_float('elasticnet__alpha', 0.001, 1.0)
    l1_ratio = trial.suggest_float('elasticnet__l1_ratio', 0.0, 1.0)
    n_neighbors = trial.suggest_int('imputer__n_neighbors', 2, 15)

    # Maak de pipeline aan
    pipeline = Pipeline([
        ('imputer', KNNImputer(n_neighbors=n_neighbors)),
        ('scaler', StandardScaler()),
        ('elasticnet', ElasticNet(alpha=alpha, l1_ratio=l1_ratio, random_state=1))
    ])

    # Evalueer met 5-fold CV (dit is de interne loop)
    #we gebruiken neg_mean_absolute_error omdat we MAE willen minimaliseren, niet maximaliseren.
    scores = cross_val_score(pipeline, X_train, y_train, cv=5, scoring='neg_mean_absolute_error', n_
    mae = -np.mean(scores) # We gebruiken neg_mean_absolute_error, dus moet het hier positief worden

    return mae

#Outer loop van de nested cross validatie
outer_mae_scores = []
outer_rmse_scores = []
outer_r2_scores = []

for fold_idx, (train_indices, test_indices) in enumerate(outer_cv.split(X, y), 1):
    X_train_outer, X_test_outer = X[train_indices], X[test_indices]
    y_train_outer, y_test_outer = y[train_indices], y[test_indices]

    # Maak een Optuna study aan. We willen de MAE minimaliseren.
    study = optuna.create_study(direction='minimize')

    #Optuna hyperparameter tuning
    study.optimize(lambda trial: objective(trial, X_train_outer, y_train_outer), n_trials=200)
```

```
    # Haal de beste parameters op
    best_params = study.best_params

    # Train het uiteindelijke model voor deze outer fold met de beste parameters
    best_pipeline = Pipeline([
        ('imputer', KNNImputer(n_neighbors=best_params['imputer__n_neighbors'])),
        ('scaler', StandardScaler()),
        ('elasticnet', ElasticNet(alpha=best_params['elasticnet__alpha'],
                                  l1_ratio=best_params['elasticnet__l1_ratio'],
                                  random_state=1))
    ])
    best_pipeline.fit(X_train_outer, y_train_outer)

    # Evalueer op de testfold
    y_pred_outer = best_pipeline.predict(X_test_outer)

    #evaluatiematen berekenen, MAE, RMSE en R^2
    fold_mae = mean_absolute_error(y_test_outer, y_pred_outer)
    outer_mae_scores.append(fold_mae)
    fold_rmse = np.sqrt(mean_squared_error(y_test_outer, y_pred_outer))
    outer_rmse_scores.append(fold_rmse)
    fold_r2 = r2_score(y_test_outer, y_pred_outer)
    outer_r2_scores.append(fold_r2)

    #printen van de resultaten per outer fold
    print(f"Fold {fold_idx}:")
    print(f"  Best gevonden hyperparameters: Alpha = {best_params['elasticnet__alpha']:.4f}, L1_ratio
    print(f"  Outer Fold MAE: {fold_mae:.2f} mmHg")
    print(f"  Outer Fold RMSE: {fold_rmse:.2f} mmHg")
    print(f"  Outer Fold R2: {fold_r2:.4f}")

standaarddeviatie_mae = np.std(outer_mae_scores)
standaarddeviatie_rmse = np.std(outer_rmse_scores)
standaarddeviatie_r2 = np.std(outer_r2_scores)

#printen eindresultaten
print("Eindresultaat pipeline 2")
print(f"Gemiddelde Nested MAE: {np.mean(outer_mae_scores):.2f} mmHg (± {standaarddeviatie_mae:.2f})")
print(f"Gemiddelde Nested RMSE: {np.mean(outer_rmse_scores):.2f} mmHg (± {standaarddeviatie_rmse:.2f
print(f"Gemiddelde Nested R^2: {np.mean(outer_r2_scores):.2f} (± {standaarddeviatie_r2:.2f})")

#Definitief model pipeline 2 trainen op volledige dataset

#Gebruik volledige dataset voor Pipeline 2
X_volledig_2 = features_data_2.values
y_volledig_2 = target_data_2.values

#objective functie
def objective_final_2(trial):
    #definieren van de hyperparameter ranges
    alpha = trial.suggest_float('elasticnet__alpha', 0.001, 1.0)
    l1_ratio = trial.suggest_float('elasticnet__l1_ratio', 0.0, 1.0)
    n_neighbors = trial.suggest_int('imputer__n_neighbors', 2, 15)
```

```
    pipeline = Pipeline([
        ('imputer', KNNImputer(n_neighbors=n_neighbors)),
        ('scaler', StandardScaler()),
        ('elasticnet', ElasticNet(alpha=alpha, l1_ratio=l1_ratio, random_state=1))
    ])

    # Evalueer met 5-fold CV over hele dataset
    scores = cross_val_score(pipeline, X_volledig_2, y_volledig_2, cv=5, scoring='neg_mean_absolute_
    return -np.mean(scores)

#optuna optimalisatie
study_final_2 = optuna.create_study(direction='minimize')
study_final_2.optimize(objective_final_2, n_trials=200)

#beste parameters printen
best_params_2 = study_final_2.best_params
print(f"\nBeste hyperparameters voor het eindmodel (Pipeline 2):")
print(f"  Alpha: {best_params_2['elasticnet__alpha']:.4f}")
print(f"  L1 Ratio: {best_params_2['elasticnet__l1_ratio']:.4f}")
print(f"  KNN Neighbors: {best_params_2['imputer__n_neighbors']}")

#definitieve model trainen op 100% van de data
final_model_pipeline2 = Pipeline([
    ('imputer', KNNImputer(n_neighbors=best_params_2['imputer__n_neighbors'])),
    ('scaler', StandardScaler()),
    ('elasticnet', ElasticNet(alpha=best_params_2['elasticnet__alpha'],
                              l1_ratio=best_params_2['elasticnet__l1_ratio'],
                              random_state=1))
])

final_model_pipeline2.fit(X_volledig_2, y_volledig_2)


# scalars ophalen
scaler = final_model_pipeline2.named_steps['scaler']
elasticnet = final_model_pipeline2.named_steps['elasticnet']
scaled_coefs = elasticnet.coef_
scaled_intercept = elasticnet.intercept_
means = scaler.mean_
scales = scaler.scale_

# Wiskundig terugschalen naar de originele schaal
unscaled_coefs = scaled_coefs / scales
unscaled_intercept = scaled_intercept - np.sum((scaled_coefs * means) / scales)

#formule printen
print("Definitieve formule voor PPG, getraind op 100% van de data:")
print("PPG =")
print(f"  {unscaled_intercept:.6f} (Intercept)")
for feature, coef in zip(features2, unscaled_coefs):
    if coef >= 0:
        print(f"  + {coef:.6f} * {feature}")
    else:
        print(f"  - {abs(coef):.6f} * {feature}")
```

```
#opgeschoonde formule printen (coëfficiënten die afgerond 0 zijn worden weggelaten)
print("Ingekorte formule:")
print("PPG =")
print(f"  {unscaled_intercept:.6f} (Intercept)")
for feature, coef in zip(features2, unscaled_coefs):
    if round(coef, 4) != 0:
        if coef >= 0:
            print(f"  + {coef:.6f} * {feature}")
        else:
            print(f"  - {abs(coef):.6f} * {feature}")
```

Code of the XGBoost model:

```
import numpy as np
import pandas as pd
import xgboost as xgb
import optuna
from sklearn.model_selection import KFold
from sklearn.metrics import mean_absolute_error, mean_squared_error, r2_score
import shap

data = pd.read_csv(r"dataset_cohort.csv", sep = ';')
data.head()

#alle ratio's en stentdiameter niet meenemen, in verslag staat waarom. Ook levercirrose niet meeneme
target = 'PPG_combi_post'
features = [col for col in data.columns if col not in ['PatientID', 'Levercirrose', 'Stent_diameter_
print(features)


#preprocessen van de data: splitsen in X en y

X_unedited = data[features]
y = data[target].values
X = X_unedited.values
feature_names = X_unedited.columns.tolist()

#definieer outer cross validation en maken lege lijsten voor het opslaan van de resultaten
#random state definieren zodat de resultaten reproduceerbaar zijn
outer_cv = KFold(n_splits=5, shuffle=True, random_state=1)
outer_mae_scores = []
outer_rmse_scores = []
outer_r2_scores = []
feature_importance = []
all_shap_values = []
all_X_test_folds = []


#outer loop van cross validatie
for fold_idx, (train_indices, test_indices) in enumerate(outer_cv.split(X, y), 1):
    # Splits de data voor deze specifieke outer fold
    X_train_outer, X_test_outer = X[train_indices], X[test_indices]
    y_train_outer, y_test_outer = y[train_indices], y[test_indices]
```

```python
#hyperparameter optimalisatie met optuna (inner loop)
def objective(trial):
    param = {
        #uitleg van elke parameter en wat log=true doet staat in het verslag.
        'learning_rate': trial.suggest_float('learning_rate', 0.001, 0.05, log=True),
        'max_depth': trial.suggest_int('max_depth', 1, 5),
        'min_child_weight': trial.suggest_int('min_child_weight', 1, 30),
        'gamma': trial.suggest_float('gamma', 0.0, 10.0),
        'subsample': trial.suggest_float('subsample', 0.5, 0.90),
        'colsample_bytree': trial.suggest_float('colsample_bytree', 0.5, 0.9),
        'reg_alpha': trial.suggest_float('reg_alpha', 0.001, 10.0, log=True),
        'reg_lambda': trial.suggest_float('reg_lambda', 0.001, 10.0, log=True),
    }



    inner_cv = KFold(n_splits=5, shuffle=True, random_state=1)
    inner_mae_scores = []
    best_iterations = []

    for inn_train_idx, inn_val_idx in inner_cv.split(X_train_outer, y_train_outer):
        X_inn_train, X_val = X_train_outer[inn_train_idx], X_train_outer[inn_val_idx]
        y_inn_train, y_val = y_train_outer[inn_train_idx], y_train_outer[inn_val_idx]

        #implementatie van early stopping zodat het model stopt met trainen als de performance n
        model = xgb.XGBRegressor(n_estimators=2000, early_stopping_rounds=200, **param, random_s
        model.fit(X_inn_train, y_inn_train, eval_set=[(X_val, y_val)], verbose=False)

        preds = model.predict(X_val)
        inner_mae_scores.append(mean_absolute_error(y_val, preds))
        best_iterations.append(model.best_iteration)
    gemiddelde_bomen = int(np.mean(best_iterations))
    trial.set_user_attr("optimal_n_estimators", gemiddelde_bomen)
    return np.mean(inner_mae_scores)

# Optuna hyperparameter search
optuna.logging.set_verbosity(optuna.logging.WARNING) # Onderdrukken van de standaard Optuna outp
study = optuna.create_study(direction='minimize')
study.optimize(objective, n_trials=200)

best_params = study.best_params
optimal_n_estimators = study.best_trial.user_attrs["optimal_n_estimators"]

best_model = xgb.XGBRegressor(
    n_estimators=optimal_n_estimators,
    **best_params,
    random_state=1,
    n_jobs=-1
)

best_model.fit(X_train_outer, y_train_outer)

# Evalueer model op de outer test set en opslaan van de MAE score en feature importance
y_pred_outer = best_model.predict(X_test_outer)
```

```
    #MAE berekenen
    fold_mae = mean_absolute_error(y_test_outer, y_pred_outer)
    outer_mae_scores.append(fold_mae)

    # RMSE berekening
    fold_rmse = np.sqrt(mean_squared_error(y_test_outer, y_pred_outer))
    outer_rmse_scores.append(fold_rmse)

    # R2 berekening
    fold_r2 = r2_score(y_test_outer, y_pred_outer)
    outer_r2_scores.append(fold_r2)

    feature_importance.append(best_model.feature_importances_)

    explainer = shap.TreeExplainer(best_model)
    shap_values = explainer.shap_values(X_test_outer)

    all_shap_values.append(shap_values)
    all_X_test_folds.append(X_test_outer)

    #printen
    print(f"Fold {fold_idx}:")
    print(f"  Beste parameters: {best_params}")
    print(f"  Aantal bomen gebruikt: {optimal_n_estimators}")
    print(f"  Outer Fold MAE  : {fold_mae:.2f} mmHg")
    print(f"  Outer Fold RMSE : {fold_rmse:.2f} mmHg")  # NIEUW
    print(f"  Outer Fold R2   : {fold_r2:.4f}")          # NIEUW

#Resultaten printen
gemiddelde_mae = np.mean(outer_mae_scores)
standaarddeviatie_mae = np.std(outer_mae_scores)
print(f"Gemiddelde MAE XGBoost model: {gemiddelde_mae:.2f} mmHg (± {standaarddeviatie_mae:.2f})")

gemiddelde_rmse = np.mean(outer_rmse_scores)
standaarddeviatie_rmse = np.std(outer_rmse_scores)
print(f"Gemiddelde RMSE XGBoost model: {gemiddelde_rmse:.2f} mmHg (± {standaarddeviatie_rmse:.2f})")

gemiddelde_r2 = np.mean(outer_r2_scores)
standaarddeviatie_r2 = np.std(outer_r2_scores)
print(f"Gemiddelde R2 XGBoost model: {gemiddelde_r2:.4f} (± {standaarddeviatie_r2:.4f})")

# Bereken het gemiddelde van de feature importances over de 5 folds
mean_importances = np.mean(feature_importance, axis=0)
importance_df = pd.DataFrame({
    'Feature': feature_names,
    'Importance': mean_importances
}).sort_values(by='Importance', ascending=False)

print("Lijst met gemiddelde feature importance (gemiddeld over de 5 folds):")
print(importance_df.to_string(index=False))

stacked_shap_values = np.vstack(all_shap_values)
stacked_X_test = np.vstack(all_X_test_folds)
```

```
# Maak er weer een net Pandas DataFrame van met de juiste kolomnamen voor de SHAP plot
X_test_df = pd.DataFrame(stacked_X_test, columns=feature_names).astype(float)

#SHAP plot
shap.summary_plot(stacked_shap_values, X_test_df)

#eindmodel trainen op 100% van de data,
X_final = data[features].values
y_final = data[target].values

# objective functie voor Optuna hyperparameter tuning
def objective(trial):
    param = {
            #zelfde hyperparameters als hierboven
            'learning_rate': trial.suggest_float('learning_rate', 0.001, 0.05, log=True),
            'max_depth': trial.suggest_int('max_depth', 1, 5),
            'min_child_weight': trial.suggest_int('min_child_weight', 1, 30),
            'gamma': trial.suggest_float('gamma', 0.0, 10.0),
            'subsample': trial.suggest_float('subsample', 0.5, 0.90),
            'colsample_bytree': trial.suggest_float('colsample_bytree', 0.5, 0.9),
            'reg_alpha': trial.suggest_float('reg_alpha', 0.001, 10.0, log=True),
            'reg_lambda': trial.suggest_float('reg_lambda', 0.001, 10.0, log=True),
        }

    # Normale 5-fold cross-validation setup voor hyperparameter tuning, geen nested CV, want evaluat
    cv = KFold(n_splits=5, shuffle=True, random_state=1)
    mae_scores = []
    best_iterations = []

    for train_idx, val_idx in cv.split(X_final, y_final):
        X_train, X_val = X_final[train_idx], X_final[val_idx]
        y_train, y_val = y_final[train_idx], y_final[val_idx]

        #early stopping om het optimale aantal bomen te bepalen
        model = xgb.XGBRegressor(n_estimators=2000, early_stopping_rounds=200, **param, random_state=
        model.fit(X_train, y_train, eval_set=[(X_val, y_val)], verbose=False)

        preds = model.predict(X_val)
        mae_scores.append(mean_absolute_error(y_val, preds))
        best_iterations.append(model.best_iteration)

    # Bereken het gemiddelde optimale aantal bomen over de folds en sla dit op
    gemiddelde_bomen = int(np.mean(best_iterations))
    trial.set_user_attr("optimal_n_estimators", gemiddelde_bomen)

    return np.mean(mae_scores)

# Optuna hyperparameter search
optuna.logging.set_verbosity(optuna.logging.WARNING)
study = optuna.create_study(direction='minimize')
study.optimize(objective, n_trials=200)

#opslaan en printen beste hyperparameters en optimaal aantal bomen
```

```
best_params = study.best_trial.params
optimal_n_estimators = study.best_trial.user_attrs["optimal_n_estimators"]
print("Beste parameters:", best_params)
print(f"Optimaal aantal bomen (n_estimators): {optimal_n_estimators}")

#eindmodel trainen op 100% van de data met de beste hyperparameters en het optimale aantal bomen
eindmodel = xgb.XGBRegressor(
    n_estimators=optimal_n_estimators,
    **best_params,
    random_state=1,
    n_jobs=-1
)
eindmodel.fit(X_final, y_final)

#model opslaan als JSON voor implementatie in app.
eindmodel.save_model("xgbModel.json")
print('Klaar met trainen eindmodel en model opgeslagen')
```

This part defines the input variables used in the application. It contains the 12 raw input features and the 5 derived ratios. These definitions are used by both prediction models, so that the linear model and the XGBoost model work with the same input structure.

```
export const FEATURE_KEYS = [
  'PPG_combi_pre',
  'BMI',
  'levervolume_ml',
  'miltvolume_ml',
  'Diameter portal vein (mm)',
  'Diameter splenic vein (mm)',
  'Diameter superior mesenteric vein',
  'Diameter arteria splenica',
  'Diameter proper hepatic artery',
  'Diameter left renal vein',
  'Slokdarmvarices',
  'Refractraire ascites',
] as const;

export type FeatureKey = (typeof FEATURE_KEYS)[number];

export const RATIO_KEYS = [
  'Spleen/liver ratio',
  'Portal vein/splenic vein ratio',
  'Superior mesenteric vein/splenic vein ratio',
  'Spleen/BMI',
  'Liver/BMI',
] as const;

export type RatioKey = (typeof RATIO_KEYS)[number];

export const RATIO_FORMULAS: Record<RatioKey, { num: string; den: string }> = {
  'Spleen/liver ratio': { num: 'miltvolume_ml', den: 'levervolume_ml' },
  'Portal vein/splenic vein ratio': { num: 'Diameter portal vein (mm)', den: 'Diameter splenic vein
  'Superior mesenteric vein/splenic vein ratio': { num: 'Diameter superior mesenteric vein', den: 'D
  'Spleen/BMI': { num: 'miltvolume_ml', den: 'BMI' },
```

```
  'Liver/BMI': { num: 'levervolume_ml', den: 'BMI' },
};

export type Inputs = Record<string, number | null>;
export type Ratios = Record<RatioKey, number | null>;

export function isNum(v: number | null | undefined): v is number {
  return typeof v === 'number' && Number.isFinite(v);
}

export function computeRatios(inputs: Inputs): Ratios {
  const r = {} as Ratios;
  for (const k of RATIO_KEYS) {
    const { num, den } = RATIO_FORMULAS[k];
    const numV = inputs[num];
    const denV = inputs[den];
    r[k] = isNum(numV) && isNum(denV) && denV > 0 ? numV / denV : null;
  }
  return r;
}
```

The second part contains the linear prediction model. It calculates the predicted portal venous pressure by adding the weighted contribution of each input variable and ratio to the model intercept. Empty fields are skipped. The model also returns the contribution of each variable, which can be used to show which inputs had the largest effect on the prediction.

```
import {
  FEATURE_KEYS,
  RATIO_KEYS,
  computeRatios,
  isNum,
  type Inputs,
  type RatioKey,
} from './features';

export type LinearModel = {
  intercept: number;
  coefficients: Record<string, number>;
  ratioCoefficients: Record<RatioKey, number>;
};

export type Contribution = { key: string; delta: number };

export type LinearResult = {
  pvp: number | null;
  filledCount: number;
  contributions: Contribution[];
};

export function predictLinear(model: LinearModel, inputs: Inputs): LinearResult {
  const contributions: Contribution[] = [];
  let pvp = model.intercept;
  let filledCount = 0;

  for (const key of FEATURE_KEYS) {
```

```
    const v = inputs[key];
    if (isNum(v)) {
      filledCount += 1;
      const delta = (model.coefficients[key] ?? 0) * v;
      pvp += delta;
      contributions.push({ key, delta });
    }
  }

  const ratios = computeRatios(inputs);
  for (const k of RATIO_KEYS) {
    const v = ratios[k];
    if (isNum(v)) {
      const delta = (model.ratioCoefficients[k] ?? 0) * v;
      pvp += delta;
      contributions.push({ key: k, delta });
    }
  }

  contributions.sort((a, b) => Math.abs(b.delta) - Math.abs(a.delta));

  if (filledCount === 0) {
    return { pvp: null, filledCount, contributions };
  }

  return { pvp: Math.max(0, pvp), filledCount, contributions };
}
```

The third part contains the XGBoost implementation. The exported XGBoost model is loaded from a JSON file and evaluated by passing the input values through each decision tree. This allows the application to calculate a prediction using the same input variables as the linear model.

```
import {
  FEATURE_KEYS,
  RATIO_KEYS,
  computeRatios,
  isNum,
  type Inputs,
  type RatioKey,
  type Ratios,
} from './features';

type RawTree = {
  left_children: number[];
  right_children: number[];
  split_indices: number[];
  split_conditions: number[];
  default_left?: number[];
};

export type XgbModel = {
  trees: RawTree[];
  baseScore: number;
  binary: boolean;
  featureNames: string[];
```

```
};

const CANONICAL_FEATURES = [...FEATURE_KEYS, ...RATIO_KEYS];
const RATIO_KEY_SET = new Set<string>(RATIO_KEYS);

export function loadXgbModel(raw: any): XgbModel {
  const learner = raw.learner;
  const param = learner.learner_model_param;
  const numFeature = Number(param.num_feature);

  const featureNames: string[] =
    Array.isArray(learner.feature_names) && learner.feature_names.length > 0
      ? learner.feature_names
      : CANONICAL_FEATURES.slice(0, numFeature);

  if (featureNames.length !== numFeature) {
    throw new Error(`feature_names (${featureNames.length}) does not match num_feature (${numFeature
  }

  const baseRaw = Array.isArray(param.base_score) ? param.base_score[0] : param.base_score;
  const objective: string = learner.objective?.name ?? 'reg:squarederror';

  return {
    trees: learner.gradient_booster.model.trees,
    baseScore: Number(baseRaw),
    binary: objective.includes('logistic') || objective.startsWith('binary:'),
    featureNames,
  };
}

function resolveFeature(name: string, inputs: Inputs, ratios: Ratios): number {
  const v = RATIO_KEY_SET.has(name) ? ratios[name as RatioKey] : inputs[name];
  return isNum(v) ? v : NaN;
}

function walkTree(tree: RawTree, features: number[]): number {
  let node = 0;
  for (;;) {
    const left = tree.left_children[node];
    const right = tree.right_children[node];
    if (left === -1 && right === -1) return tree.split_conditions[node];

    const x = features[tree.split_indices[node]];
    const goLeft = Number.isNaN(x)
      ? (tree.default_left?.[node] ?? 1) !== 0
      : x < tree.split_conditions[node];

    node = goLeft ? left : right;
  }
}

const sigmoid = (x: number) => 1 / (1 + Math.exp(-x));
const logit = (p: number) => (p <= 0 ? -15 : p >= 1 ? 15 : Math.log(p / (1 - p)));
```

```ts
export function predictXgb(model: XgbModel, inputs: Inputs): number | null {
  if (!FEATURE_KEYS.some((k) => isNum(inputs[k]))) return null;

  const ratios = computeRatios(inputs);
  const features = model.featureNames.map((n) => resolveFeature(n, inputs, ratios));

  let margin = model.binary ? logit(model.baseScore) : model.baseScore;
  for (const tree of model.trees) margin += walkTree(tree, features);

  return model.binary ? sigmoid(margin) : Math.max(0, margin);
}
```

M Application layout

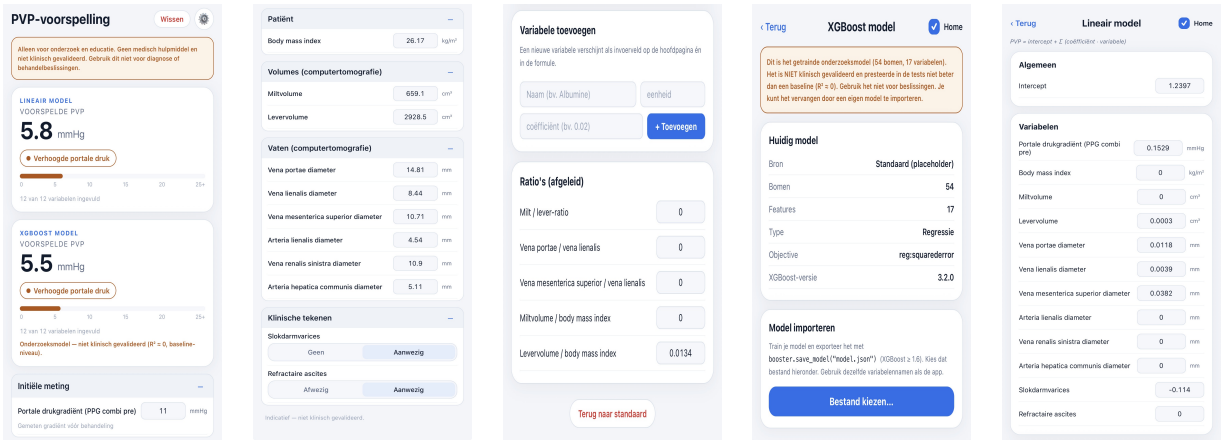

Figure 6: Overview of the application screenshots.