BACHELOR THESIS TECHNICAL MEDICINE

The ratio between tumor volume, resected liver volume and the remaining liver volume, determined by CT volumetry: A new prospective factor in predicting Posthepatectomy Liver Failure (PHLF)?

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Date:
June 20th 2016

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We would like to express our gratitude for our supervisors during this project. Without their help and guidance this study would not have been possible. The discussion, ideas, and feedback have been absolutely invaluable.

Thanks to the people involved with this thesis:

Dr. K.P. De Jong

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Abstract

Introduction: Posthepatectomy Liver Failure (PHLF) is a serious complication that can occur after a partial liver resection. The ratio described by the remaining functional liver tissue in relation to the amount of functional liver parenchyma that is resected may play a part in predicting PHLF.

$$\text{Ratio} = \left(\frac{Residualvolume}{Residualvolume+Resectedvolume-Tumorvolume}\right)$$

Method: CT-images of 12 patients were segmented and a volumetric determination of the total liver, left lobe, right lobe and the tumor was done by using Matlab. These volumes were analyzed, by a Pearson's correlation in SPSS, in relation to the Area Under the Curve (AUC) of Prothrombin Time (PT) and the Total Bilirubin (TB) from day one until ten.
Results: A Pearson's correlation of R=0.557 (p=0.060), a moderate positive correlation, was found between the AUC of the AUC of PT and the ratio of the functional resected liver volume and the remaining functional liver tissue. A moderate negative correlation (R=-0.497, p=0.100) was found between the AUC of TB and the ratio.
Conclusion: Although not significant it is interesting to see a negative correlation between the described ratio and the AUC of TB. More research is needed to further evaluate the effect of this ratio. This new predictive factor could prove valuable and may help bring down medical costs further and improve patient well being.

Contents

1 Introduction

According to the Dutch Institute for Clinical Auditing (DICA) in 2014 there were 1443 partial liver resections done in 27 participating hospitals.[1] Posthepatectomy Liver Failure (PHLF) is a severe complication that can occur after a partial liver resection. In the worst case scenario PHLF leads to death. In less severe cases PHLF causes an extended hospitalization time and extra therapeutic and diagnostic measures. Even though PHLF only occurs after 10% of all liver resections, the consequences of PHLF have a tremendous impact on the patients well-being.[2]

Various studies have been conducted in hope of determining risk factors for developing PHLF. These risk factors include: diabetes mellitus, seniority, preoperative chemotherapy, hepatitis, fibrosis, cirrhosis and a small Future Liver Remnant (FLR).[3–5] Comparing research is difficult because a uniform definition of PHLF is not yet agreed upon.[6]

When a patient's FLR is predicted to be less than 20% most surgeons choose not to perform surgery because this FLR is deemed to be too small.[5] This percentage ignores tumor size in its evaluation, disregarding the effects of having a large or small tumor. Limited research has been conducted on the effect on PHLF caused by the amount of healthy tissue removed in relation to the total resection volume. Researching this effect could prove valuable to both the hospital and patient.

1.1 Reading guide

This report will not follow the standard model of a research paper. The method is replaced by the process evaluation. The process evaluation will give a chronological overview of all the steps made in order to arrive at the final method.

This reading guide will provide a short overview of this study. Chapter 2 describes the problem and introduces the objective and approaches. Anatomy and physiology of the liver, liver resection and PHLF are described in chapter 3. The hypothesis of this study is discussed in chapter 4. The process evaluation is described in chapter 5. The results that are given before "chapter 6: Results" are results that led to new insights and adjustments to the approach. The final approach that was used can be found under 5.3.5. The results are shown in chapter 6. Chapter 7 will draw conclusions from the results and are these are discussed in chapter 8. The recommendations for future research are shown in chapter 9. References are shown in chapter 10. The appendices are found in chapter 11.

All abbreviations used in this thesis are summarized in appendix A.

2 Objective and approaches

The literature describes a collection of risk factors that affect PHLF.[3–5] In addition to these risk factors this study investigates a new possible risk factor in developing PHLF. This possible risk factor is: the tumor volume in relation to the amount of resected liver volume, linked to the FLR.

The extend of this risk factor is depicted in figure 1. Both tumors in this example will be treated similarly, with a right hemihepatectomy. In example A, more healthy liver will be resected compared to example B, where a relatively low amount of healthy liver tissue will be removed. When FLR is used to predict the chance of developing PHLF, this difference in the amount of healthy liver parenchyma resected is not taken into account. This study will explore if there is any difference in the outcome of patient A and B when they receive similar treatment.

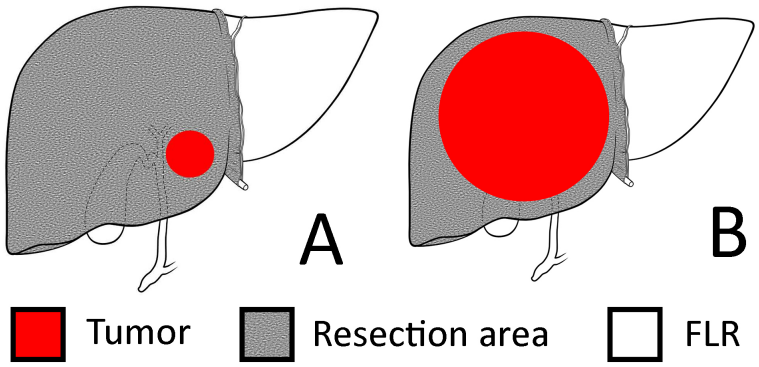


Figure 1: The extend of the risk factor described by the tumor volume in proportion to the liver volume. A: Patient with a relatively small tumor. B: Patient with a relatively big tumor.

According to protocol patients who undergo a hemihepatectomy also undergo a preoperative contrast enhanced Computed Tomography (CT)-scan.[7] CT based analysis of these scans is used to give an accurate estimation of the the resection volume, tumor volume and the FLR.[8] To investigate the relation between these volumes and the development of PHLF, this study will utilize these accurate estimations derived from these CT-images.

This unevaluated risk factor prompted the following research question:

Is it possible to predict the development PHLF in patients who receive a right hemihepatectomy by using a ratio between tumor volume, resected liver volume and the remaining liver volume acquired by CT?

The following sub-questions are derived from the main research question:

- What is the definition of PHLF and how do we measure this?
- How do we determine the volumes of the liver, tumor and resection area from the CT-images?
- How do we shape a database based upon relevant parameters?
- How do we analyse the statistical and clinical relevance of the results?

3 Background

3.1 Anatomy and physiology of the liver

The liver is the second largest organ of the human body. The liver has a major role in the fat-, carbohydrate- and protein-metabolism. Besides its metabolic functions, the liver also has the function to store glycogen and excrete bile.[9]

The liver is divided in eight segments by various vascular structures, these structures are visible in figure 2.[10] These liver segments consist of many different liver lobules. A liver lobule is a small sub unit of the liver that consist of a branch of the portal vein, a branch of the hepatic artery, a branch of the hepatic vein and a bile duct.[10]

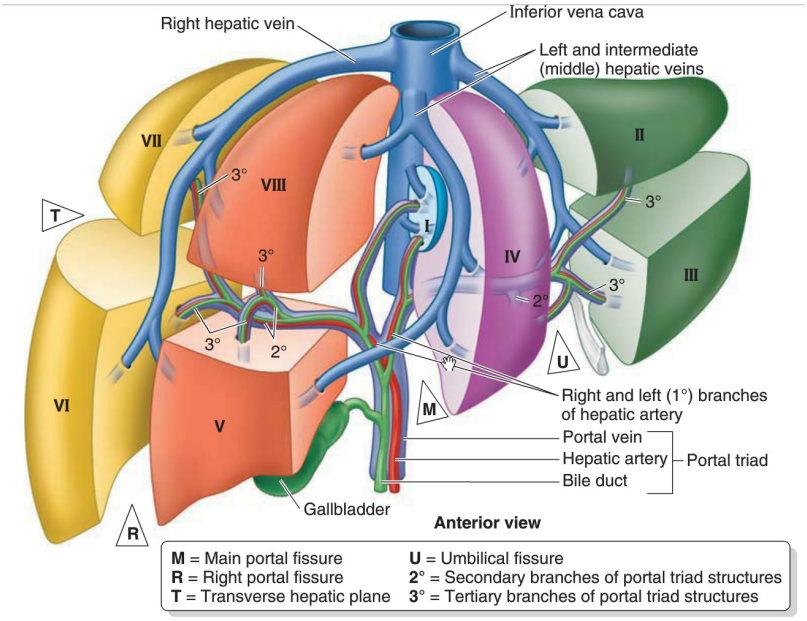


Figure 2: An explanation of the eight liver segments and the vascular structures [10]

The hepatocytes break down the substances that are delivered in the liver from the small intestine through the portal vein.[9] A big part of the liver, as much as 90%, consist of hepatocytes. The hepatocyte has a broad spectrum of functions; it produces and secretes substances, it assimilates and stores substances and it digests, detoxifies and synthesizes substances. The hepatocyte excretes proteins like bilirubin and produces proteins such as prothrombin, albumin, fibrinogen and other clotting factors. Carbohydrates and lipids are stored in hepatocytes as glycogen and fat droplets. Hepatocytes are long living cells with a low mitotic index, contradictory to this low index value the liver has an excellent regenerative ability after loss of functioning liver parenchyma. The cause of this phenomenon is the extremely high mitotic rate of the remaining cells in the liver .[11]

3.2 Liver resection

Liver tumors can have various origins. Colorectal Liver Metastasis (CRLM), a primary Hepatocellular Carcinoma (HCC) and an Intrahepatic Cholangiocarcinoma (ICC) are the most common tumors of the liver. Usually the treatment of all liver tumors is similar despite these different origins. Most of these tumors are treated with a curative resection.[12]

The tumor location is determinative for the required operation. Tumor cells from the primary colorectal tumor can travel to the liver from the colon trough the portal vein giving rise to CRLM. Because of the blood flow in the portal vein, most metastases reside near the right branch of the hepatic portal vein in the right side of the liver.[13] A right hemihepatectomy is necessary when a tumor resides near this right branch of the hepatic portal vein. Usually the tumor does not make up most of the right lobe therefore a lot of functional liver tissue is removed during this hemihepatectomy. This major loss of functional liver tissue may be the cause of complications. The mortality for metastatic disease is $<5\%$ and for HCC it is $<10\%$ when treated in centers where they specialize in liver resections.[3]

A FLR of at least 20% is commonly used as a safe threshold when preforming a liver resection.[14] When the liver tissue is affected by diseases like cirrhosis and hepatic steatosis a higher threshold is used (30-40%).[5] A resection is not recommended when the FLR falls below this threshold and is deemed to small to function. To solve this problem a Portal Vein Embolisation (PVE) can be done. This procedure may result in hyperplasia of the tissue in the left liver lobe and thus a larger FLR.[15–17]

3.3 Posthepatectomy Liver Failure

After patients receive a hemihepatectomy there is a change that they develop PHLF. Because a uniform definition and gradation of PHLF is lacking in current literature, difficulties arise when researching PHLF. There are a number of definitions proposed in the literature.[6] Most of these studies make use of postoperative lab results, such as Total Bilirubin (TB) and Prothrombin Time (PT), and clinical management to define PHLF. Some of the definitions for PHLF are summarized in table 1. Postoperative blood proteins, like albumin and fibrinogen, were not described in the literature as predictive proteins for the development of PHLF.

Research authors	**Measuring moment**	**Total Bilirubin (μmol/L)**	**Prothrombin Time (s)**
Balzan 2005[18]	POD 5	> 50	PT$>$18
Mullen 2007[19]	Peak value	> 120	n.a.
Rabhari 2011[6]	$>$ POD 5	UMCG protocol: > 17	UMCG Protcol: > 12 sec

Table 1: Comparing definitions of Posthepatectomy Liver Failure (PHLF) as proposed by Balzan et al. Mullen et al. and Rabhari et al. measuring moments most commonly used are post-operative day five (POD 5) and the peak value. Rabhari et al. uses the cutoff values as defined by the local labaratory. Therefore in this study the cutoff values of the University Medical Center Groningen (UMCG) are used.

3.3.1 Total Bilirubin

Bilirubin is a breakdown product of hemoglobin. Bilirubin is fat soluble and it is hydrophobic. To transport bilirubin through the blood it is covalently bound to albumin. When these two substances arive in the liver they are seperated into bilirubin and albumine. The bilirubin is altered in the hepatocyte to conjugated, or direct, bilirubin. Direct bilirubin is hydrophilic and is transported out of the cell and into the bileducts via an Adenosine Triphosphate (ATP)- dependent pathway. This ATP-dependent pathway experiences dysfunction when a patient suffers from PHLF, resulting in a raised serum bilirubine. Serum bilirubin consist of direct bilirubin and unconjugated, or indirect, bilurubin. These two parameters together are called the TB.[20]

3.3.2 Prothrombin Time

The liver produces almost all clotting factors. The production of these clotting factors is decreased when the liver function is reduced. This results in a longer coagulation time. PT is the time it takes for blood to clot. The PT can be determined in various manners, which vary per hospital. The International Normalized Ratio (INR) standardizes these different PT's.[20]

3.3.3 Clinical management

Patients who suffer from PHLF do not only have a raised INR and bilirubin. Clinically these patients show signs of hepatic encephalopathy, icterus, coagulation disorders, kidney insufficiency and multi-organ failure.[21] Liver failure occurs after 10% of the hemihepatecomies. Besides this morbidity rate there is also a mortality rate of 30%.[2]

4 Hypothesis

When a hemihepatectomy is performed it is often necessary to resect a large portion of functional liver tissue. This is due to the anatomy of the blood supply to the liver. For example a small tumor, near the right branche of the portal vein, can lead to a resection of the entire right lobe; a right hemihepatectomy.[10]

CRLMs make up 62% of all malignant liver tumors.[22] Due to the functional anatomy of the liver, most of these metastasis take root near the right branch of the portal vein in the right liver lobe.[13] One would expect the CRLM to oppress the hepatocytes and that this would show in the dysfunction of the liver. However patients with a tumor as big as the entire right lobe do not experience liver dysfunction. Because these patients do not experience liver dysfunction it is to be expected that the healthy hepatocytes in the unaffected lobe make up for most of the loss of function through hyperplasia or through overcapacity.

This leads to the presumption that the consequences of a right hemihepatectomy are more profound with small tumors. With small tumors it is not/less necessary for the not-affected lobe to account for the loss of function of the liver.

This expectation can be expressed in a ratio between tumor volume, resected liver volume and the remaining liver volume. This ratio takes the the tumor volume into account in relation to the volume of the resected part of the liver and the FLR. A low ratio expresses a neglectable tumor size relative to the resected tissue, because this is nearly all healthy tissue. A high ratio expresses that the tumor is almost as big as the resected volume. We expect that this ratio can be a prospective factor in predicting PHLF. The higher the ratio, the lower the chance to PHLF occurring after a right hemihepatectomy.

This expectation can be translated in the following hypothesis:
The ratio between tumor volume, resected liver volume and the remaining liver volume is a prospective risk factor in predicting PHLF

Adding this new prospective factor for PHLF, could result in better treatment planning and thus a better outcome for patients, a better quality of life and a shorter hospitalization time. Numbers of mortality and morbidity could be reduced and the cost effectiveness of the hemihepatectomy increased.

5 Process evaluation

5.1 Phase A: Inclusion and exclusion of the patients

This study functions as a pilot study and was commissioned by the UMCG. A list was created containing patients who underwent a right hemihepatectomy from 1988 until 2015. This list was evaluated by starting with the most recent hemihepatectomy and working toward the hemihepatectomies in the past. Because of the limited time frame only patients were included if the patients underwent a right hemihepatectomy in the period April 2008 - July 2015. Fifty-six patients were included in the database and given a unique number. Their names and patient numbers linked to the data set in the UMCG were held in a separate list in order to assure patient confidentiality and anonymity.

In order to create an homogeneous and functional research population, patients who matched the following criteria were excluded:

- A CRLM or ICC was not presented in the right liver lobe of the patient;
- A preoperative CT-scan of the total liver was not available;
- The clinical follow-up after hemihepatectomy was not recorded or not available;
- Preoperative ablation therapy was performed;
- Suffering from PHLF induced by another cause, such as intoxication as a result of medication use.

HCCs were not evaluated because these carcinomas consist of mutated hepatocytes. Therefor the tumor could still have some functional potential. Neuroendocrine metastasis in the liver releases hormones that could disturb the hepatic function therefore patients with these tumors were excluded. Because of the design of the study (pilot study) only CRLMs and ICCs were evaluated for the sake of homogeneity and reasons listed above.

If patients previously received liver related surgery they were also excluded as could be of influence of the results.

These exclusion criteria resulted in the exclusion of twelve patients. All meaningful parameters (described in appendix B) were included into the database of the research population of 44 patients. PT and TB were chosen as parameters that would be evaluated.

Albumin and fibrinogen were not deemed usable. It is to be expected that, because of the loss of functional liver parenchyma, the albumin and fibrinogen concentration will decrease. But this effect is overshadowed because albumin and fibrinogen are acute phase proteins. The albumin concentration decreases due the onset of the acute phase. The concentration of fibrinogen increases in the acute phase. The onset of the acute phase takes place due every sort of inflammation and therefore albumin and fibrinogen are not usable for this study.

5.1.1 Nineteen patients

The group of 44 patients was evaluated and was found too heterogeneous for further research. A new set of exclusion criteria were necessary to obtain a heterogeneous patients group. Patients were excluded from the study for the following reasons:

- The patient suffered from more than one tumor in the liver. Patients with one tumor were included to keep the group homogeneous as possible;
- The CT-images of a patient were of poor quality and not usable for determining the liver volumes, for example no contrast was used whereby Veins and arteries were not visible on these CT-images. Due to this deficiency the separation of the right and left lobe was not possible.

Twenty-five patients were removed from the study due these exclusion criteria. In the residual group nineteen patients were included. Statistical analysis is performed on this patient group.

5.1.2 Eleven patients

The group of nineteen patients was not homogeneous enough because eight patients suffered from severe liver related diseases or systemically sicknesses. These diseases could influence the health of the patient en therefore health state of the FLR. The following patients were excluded from the study for the following reasons:

- Suffering from a severe liver related sickness or disease postoperatively; like bile leakage and collection of fluid around the resection plane. These diseases could influence the state of the parenchyma and therefore disturb the blood values;
- Suffering from a severe systemically related sickness or disease postoperatively. These diseases could influence the health status of the patient, therefore influence the liver status and thereby disturb the blood values;
- Suffering preoperatively from a sickness or disease that could influence the blood values of PT and/or TB;
- A postoperative laparotomy was performed.

Patients were not excluded if they suffered from kidney failure. This was done because kidney failure is a postoperative disease, but is not caused by liver failure. The contrast of the CT-scan could disturb kidney function (including kidney failure). This phenomenon has limited influence on the blood values and therefore these patients were not excluded.

The patient group diminished to eleven patients. Statistical analysis was performed on this patient group.

5.1.3 Twelve patients

A group of eleven patients is a fairly small patient group. To expand the group, nine more patients were evaluated from the period July 2015 - December 2015. From these nine patients only one could be included to the study. The other eight patients were excluded for multiple reasons described in the exclusion criteria above.

Eventually twelve patients were included. This patient group was used in the final statistic analysis.

5.2 Phase B: Analysis of the CT-images

To obtain volumetric specification of the patient's liver, tumor and the amount of resected tissue, CT-images were processed in MatlabR2016a (MathWorks, Massachusetts, United States). Determining the volumes through CT-images is a validated method in which the predetermined resection volume match the actual resected volume.[8] The Matlab script written and used for this study can be found in appendices E through J.

5.2.1 Segmentation of the Liver

The goal of the segmentation process was to get an accurate estimation of the liver and tumor volumes. To design the script to fulfill this goal, criteria were drafted beforehand. The script must meet the following criteria:

- Visualize the CT-scan;
- Segment the tumor tissue from the rest of the scan;
- Be able to divide the liver in the right and left lobe;
- Be able to determine the volume of the tumor and the two lobes.

CT data received from the UMCG was stored in the Digital Imaging and Communications in Medicine (DICOM) file format. In order to do volumetric calculations these DICOM files had to be loaded into Matlab. This was done by loading each individual slice into a 3D array (appendix E line 10 trough 32) This 3D array contained the gray scale values of the CT-Scan. Slices in which liver tissue was present, were manually selected and extracted (appendix E line 49 trough 56). The slices in which no liver tissue was present were disregarded. This patient specific 3D array and image window were stored in a .mat file labeled with the patient number (appendix E line 57 trough 70).

After loading and labeling the entire CT-data set, segmentation of the liver and tumor could commence. Firstly the rough shape of the liver was obtained by thresholding. By looking at the density distribution histogram of each specific CT-scan, lower and upper grayscale bounds were determined. In most images the grayscale values of tissues were located between the 800 and the 1300 mark (figure 3a). All values out of these bounds were changed to zero and all values that were in between the specified grayscale bounds were changed to one. By doing this a black and white mask was created (figure 3b, appendix F line 11 trough 44). This black and white mask of the liver was used for further segmentation operations.

Because slices that did not contain liver tissue were already removed from the image stack, the biggest three dimensional volume in the image stack is the liver. This trait was used to try and remove any non-liver tissue present in the created black and white mask. In order to segment based on largest volume it is important that the liver is not in any way connected to non-liver tissue. If it is connected to non-liver tissue, Matlab will regard this non-liver tissue as liver tissue and the segmentation will not be valid.

To increase the likelihood that the liver is not connected to different tissue, various commands were used. The matlab commands *imopen, bwlabeln, regionprops, ismember, imdilate* and *imerode* were combined with specific structuring elements to mold the mask of the liver (appendix F line 24 trough 38). These commands will be specified below.

The *imopen* command conducts morphological opening on the mask (figure 3c). After the image was morphologically opened the *bwlabeln* command was used to label pixels in the mask. Labeling was needed to look up the properties of connected volumes. All the pixels that were not a member of the group with the largest volumes were changed to zero using the command ismember and regionprops (figure 3d).

To account for non-homogeneity in the liver the *imdilate* and *imerode* commands were used (using the same structuring element) (figure 3e trough figure 3f). The next step was slice-by-slice evaluation of the created mask. In some patients elements, such as the kidneys or part of the colon, were still connected to the liver in some slices. A variation of the previous commands was executed on sections in which these elements were not connected to remove them from the segmentation (figure 3g, appendix F 40-114).

Final step was using imtool3D to view the segmentation as an overlay and use the smart brush to manually adjust sections of the segmentation that were not a good representation of the liver (figure 3h, appendix G). Sometimes the tumor tissue was hard to detect. Applying a color filter, from a gray scale to a orange/red scale called 'hot', helped to distinguish the tumor tissue from the healthy tissue.

5.2.2 Segmentation of the tumor

The same process was repeated for the tumor using a slight variation on the code. In addition to the previous steps the x, y and z bounds of the tumor had to be defined (appendix F line 116 trough 234). In most of the CT-images that were reviewed the tumor was surrounded by healthy liver tissue. Because the intensity level between these two tissue types is quite large, it was relatively easy to segment these tumors. When a tumor was larger and was located on the edge of the liver, segmentation was significantly more difficult. This was because the tumor tissue mask connected to the non-tumor mask. These larger tumors near the edge needed more manual adjusting than their smaller, centered, counterparts as seen in figure 4a trough d.

5.2.3 Division of the left and right liver lobe

Division of the right and left lobe was done by finding the Middle Hepatic Vein (MHV) through evaluation of the CT-images (appendix H line 16). By specifying two points a line was created through the MHV (appendix H line 19 trough line 29). This line was used to create a plane that divided the liver into two parts, respectively the right and left lobe (appendix H line 32 trough 62).

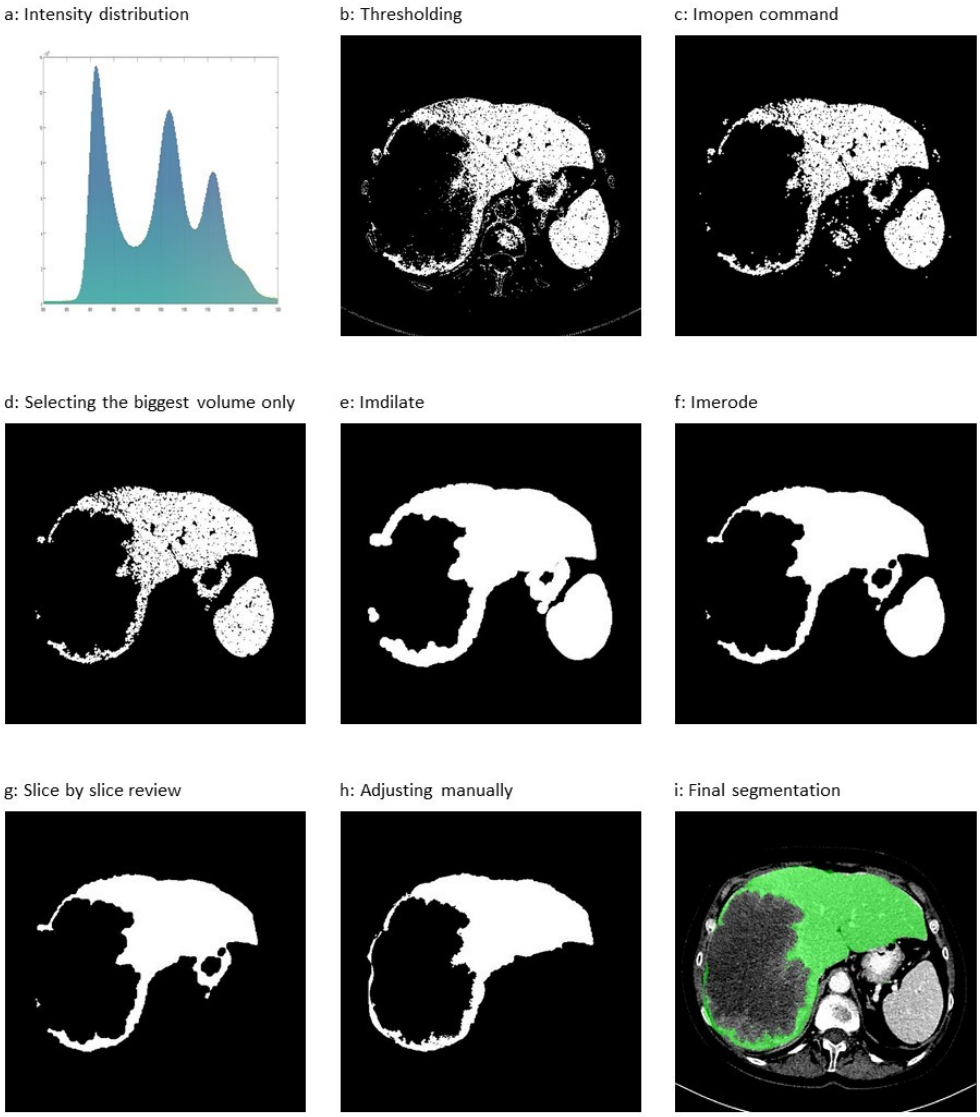


Figure 3: Figure a trough i: a 2D visualization of the 3D steps described in section 5.2.1

5.2.4 Volumetric analysis

The sum of all elements, that were not zero in the 3D array, was calculated using the matlab function *nnz*. This number was multiplied with the voxel size of each specific scan (appendix I line 1 trough 31). This gave a volume in mm^3, this was divided by 1000 in order to display the results in cm^3, which is more convenient because the volume in cm^3 is roughly equal to the weight in grams. The volume of the total liver, the volume of the right lobe, the volume of the left lobe and the volume of the tumor were determined this way.

In order to evaluate the precision of this method four observers segmented the same CT-scan and the results were compared by relative differences as shown in table 2. After noticing significant differences in the volumetric outcome causes were explored and rules were drafted. One of the rules was that scans that differed more than 5% would be reevaluated.

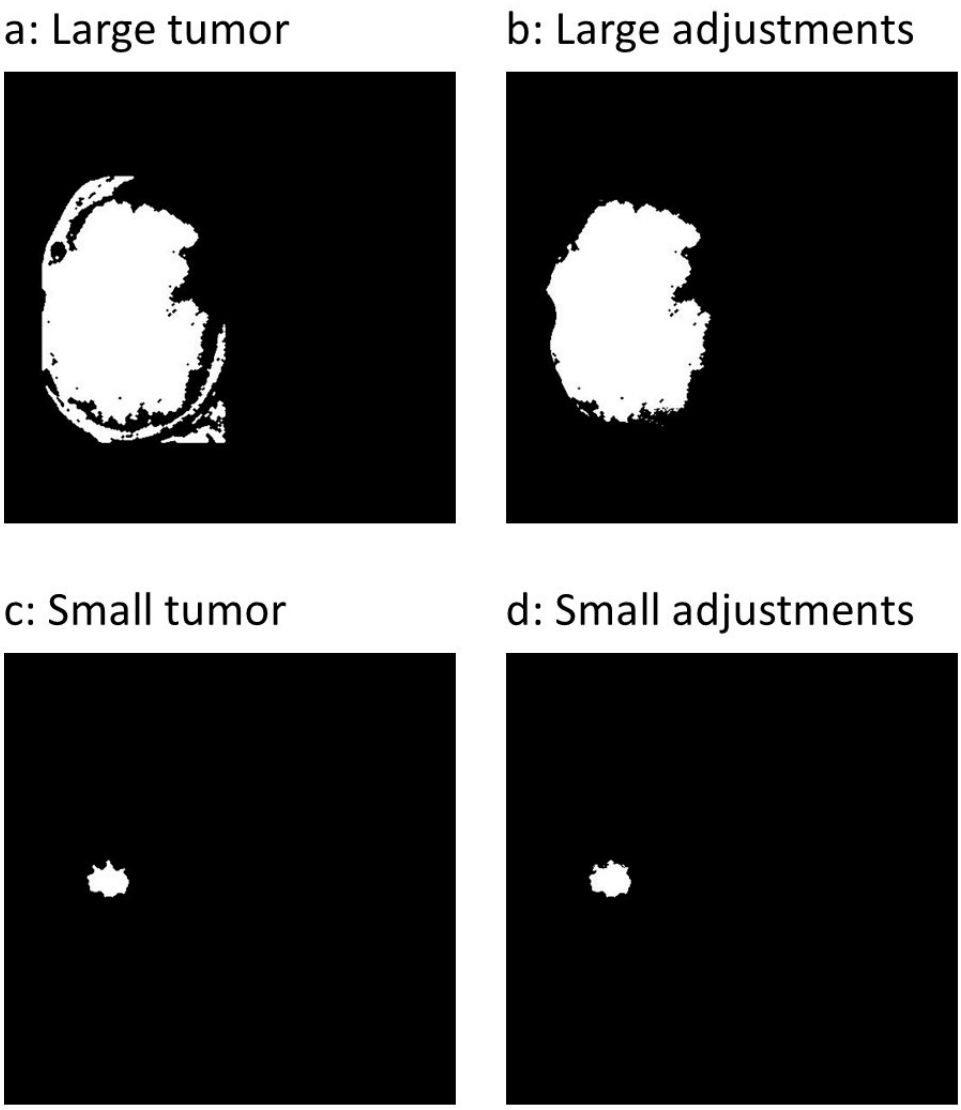


Figure 4: Difference in tumor segmentation. a and c before manually adjusting, b and d after manually adjusting.

	Observer 1	**Observer 2**	**Observer 3**	**Observer 4**	**Mean**	**Diff**
LL+LR (cm^3)	1852	1908	1938	1973	1918	6.14
LR (cm^3)	929	888	910	927	913	4.45
LL (cm^3)	1021	1020	1029	1046	1029	2.50
T (cm^3)	2023	2040	2034	2017	2029	1.14

Table 2: Differences in results between observers in total liver volume (LL+LR), Liver Right volume (LR), Liver Left volume (LL) and Tumor volume (T) displayed in cm^3. The last column displays the maximum difference in %.

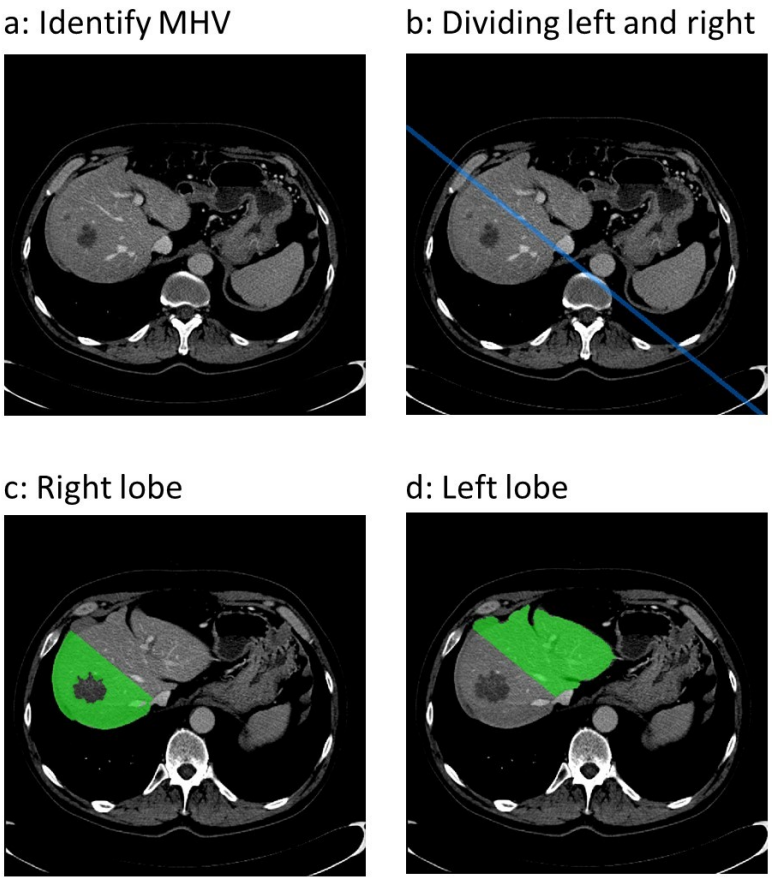


Figure 5: Process of the lobe division. (a): A slice were the Middle Hepatic Vein (MHV) is clearly visible. (b): Drawing a line through the entire slice. (c): The volume of the right lobe (LR). (d): The volume of the left lobe (LL).

Because of the limited time frame it was decided that in the future every CT-scan would only be segmented by two people instead of four, but the stricter segmenting criteria drafted from the test case would be applied.

After determining the various volumes the relative differences were compared. If the 5% threshold was surpassed there were four possible reasons and consequences:

- One observer had taken margins that were to small and the other observer had taken to big of a margin. This was resolved by adopting the average of the two volumes;
- There was no clear difference in the two segmentations. This was resolved by doing a third segmentation;
- One of the segmentations was done incorrectly. This was resolved by correcting this segmentation;
- If the segmentations was deviant and the reason for the difference was not clear the opinion of a professional was asked.

5.3 Phase C: Statistical data analysis

This section will give a detailed chronological overview of all the steps made in order to arrive at the final results. Results obtained and mentioned before "chapter 6: Results", were results that led to new insights and adjustments to the approach. These adjustments in the approach caused changes in population size and changes in definition of the described ratio. The final method used to attain our final results can be found in 5.3.5.

All statistical analysis were performed using IBM SPSS Statistics version 23 (IBM Corporation, Chicago, United States).

5.3.1 Statistical method

The bivariate Pearson's Correlation is used to determine the strength and direction of the linear relationships between pairs of normally distributed variables. To interpret the outcomes of the Pearson's correlation coefficient table 3 is used.[23] A 95% confidence interval will be used therefore $p<0.05$ is significant.

To determine how well the model fits the data, a scatter plot is used to calculate the R-squared (R^2). R^2 is used to measure how close the data are fitted to the regression line. It is the percentage of the response variable variation that is explained by a linear model. A result of 0% indicates that the model explains none of the variability of the response data around its mean. A 100% indicates that the model explains all the variability of the response data around its mean.

Because the bivariate Pearson correlation cannot address non-linear relationships a Spearman's correlation was considered. Spearman's correlation assesses monotonic relationships, whether linear or not. This means that if the two variables are monotonically related, all data-points with greater x-values than that of a given data-point will have greater y-values as well. Due to the small population a Pearson's Correlation is preferred above a Spearman's correlation.[24] The Pearson's Correlation is therefore used in this study.

Size of Correlation	**Interpretation**
(-).90 to (-)1.00	Very high positive (negative) correlation
(-).70 to (-).90	High positive (negative) correlation
(-).50 to (-).70	Moderate positive (negative) correlation
(-).30 to (-).50	Low positive (negative) correlation
0.00 to (-).30	Negligible correlation

Table 3: Interpretation of the magnitude of Pearson's correlation.[25]

5.3.2 Definition of liver volumes

In figure 6 the abbreviation of each segment of the liver can be found. These abbreviations will be used throughout section 5.3 to describe the various ratios that were used.

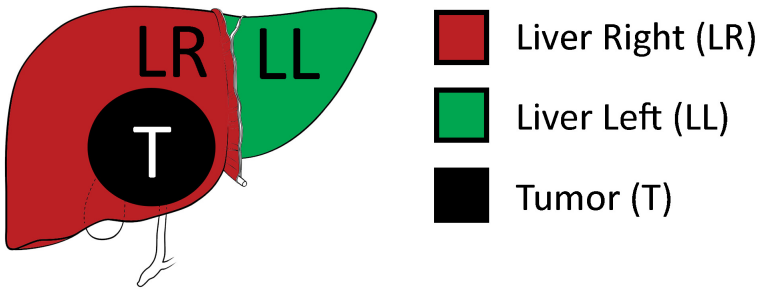


Figure 6: Visualization of the volumes in the liver. Tumor volume (T), the resected liver volume (T+LR) and the remaining liver volume (LL).

5.3.3 Group of nineteen patients

This first section will focus on the statistical analysis that was performed on the group of nineteen patients described in 5.1.1.

The database consisted of nineteen patients with the parameters as described in appendix B and the liver volumes calculated in phase B (5.2). The definition of ratio at the time was:

$$\text{Ratio} = \frac{T*FLR}{T+LR}$$

In order to interpreted PT and TB values Microsoft Office Excel 2016 (Microsoft, Redmond, United States) was used to calculate and plot the means and standard deviations of day one until day ten, visible in figure 7. Changes in PT and/or TB after ten days are usually caused by factors other than PHLF. Because this study's aim is to evaluate the effect of factors tied to the size of the tumor and not the effect of additional complications, only the first ten days will be evaluated.

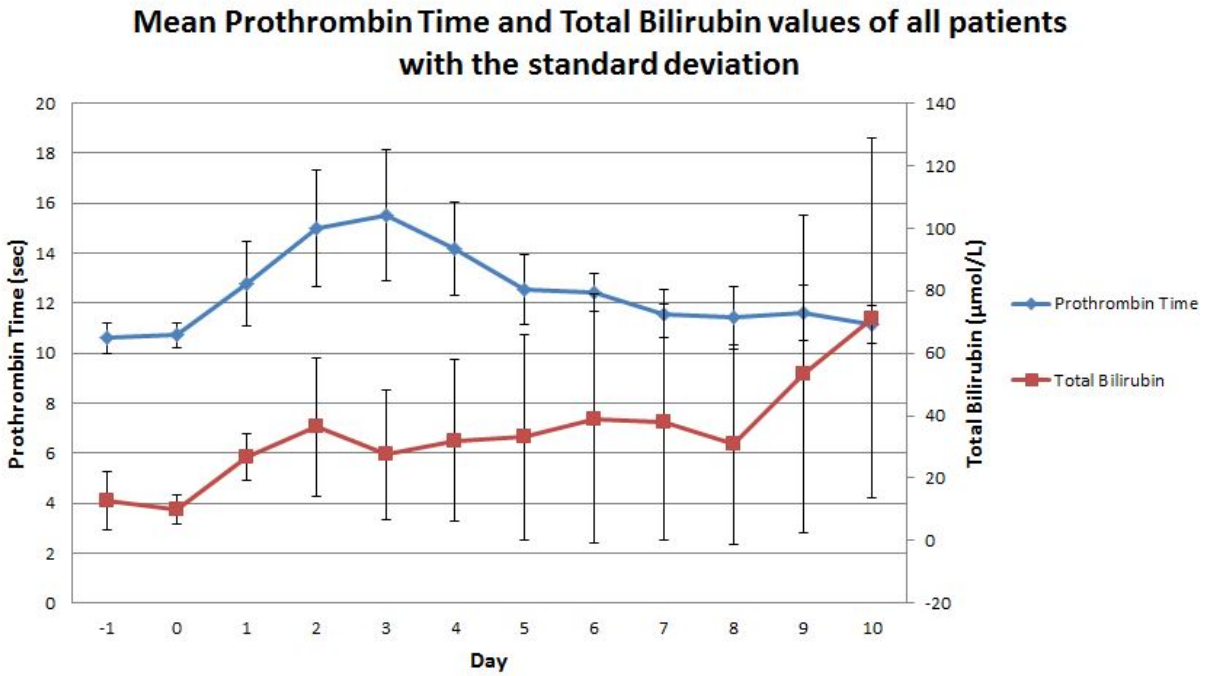


Figure 7: In this figure the mean Prothrombin Time (PT) and Total Bilirubin (TB) values of the nineteen patients are displayed together with the standard deviation. Day minus one = a week before surgery, day zero = a day before surgery and day one = directly after surgery. Note: the PT value of patient 24 on day minus one was deleted for this figure, because the PT was effected by the use of oral anti-coagulation by the patient.

Remarkable findings in figure 7:

- The average peak of PT is on the third day;
- On day minus one (a week before surgery) and day zero (a day before surgery) the standard deviation of the average between the patients is small;
- the standard deviations get larger as the days advance;
- From day eight until ten the average TB rises.

These phenomena could be explained by a few factors. The increase and decrease of PT could be explained by the trauma related with surgery.[26] The small standard deviations in day one and day minus one could be an indication that the liver function of the patients was similar although their tumors differed in size. The growing of the standard deviation means the patients react to the treatment differently. The difference could be their FLR or the amount of healthy tissue that was lost.

Because the aim of this study is to determine if there is a correlation between PHLF and the ratio it is crucial to determine which variables are compared. PT and TB will be compared with the ratio and FLR. PT and TB was also compared to FLR because FLR is currently the standard parameter in determining if a patient is likely to develop PHLF. If the ratio shows a stronger correlation than PHLF with PT or TB this could be an indication that the ratio is a good addition when assessing the risk of developing PHLF. If the hypothesis is true it is to be expected that TB and PT are negatively correlated with the ratio.

In order to test the presence of a linear correlation the Pearson's correlation test was used. The significant results of this test can be found in the table in figure 8, all the results can be found in appendices K and L.

Correlations

	Ratio T/LR * FLR	Functional Liver Remnant = LL/(LL+LR+T)
Prothrombin Time on day 1	.836	-.075
	.000	.783
	16	16
Prothrombin Time on day 5	.661	-.102
	.019	.753
	12	12

Figure 8: The Pearson's correlation between Prothrombin Time (PT) on day one and day five and the ratio and the Pearson's correlation between these values and Functional Liver Remnant (FLR).

The results are not in line with the hypothesis. A strong correlation between the ratio and PT is observed on day one and five but this correlation is positive meaning that the higher the ratio (a larger tumor) the higher PT. All other values were not deemed significant. When evaluating TB on day ten and FLR a strong negative (R=-0.800) significant (p=0.031) correlation is observed, meaning that a larger FLR means a lower TB on day ten.

The maximum values of PT and TB were also taken into account to study the correlation between the ratio and the peak values of PT and TB. TB did not give any significant result PT gave a significant (p=0.018) positive correlation (R=0.537) as shown in figure 9.

Correlations

	Ratio T/LR * FLR	Functional Liver Remnant = LL/(LL+LR+T)
Max Prothrombin Time value	.537	-.174
	.018	.476
	19	19
Max total Bilirubin value	-.130	-.262
	.597	.278
	19	19

Figure 9: The Pearson's correlation between the ratio and Functional Liver Remnant (FLR) and the peak values of Prothrombin Time (PT) and Total Bilirubin (TB).

The fact that the peak value of PT does not describe the course for the other days. This combined with the fact that trauma causes a rise in PT was the reason to try different approaches for finding a correlation with the ratio.

In order to determine if the ratio has any effect on patient health the goal in this segment is to evaluate the correlation between hospitalization time and the blood values. The presumption is is made that patients with a high PT and/or a high TB value are sick. Another presumption is that patients with a long hospitalization time are also sick. The expected result is that patients with a high PT and/or TB have a longer hospitalization time. In order to study the correlation between hospitalization time and the PT and TB values a bivariate Pearson's correlation is performed.

The table in figure 10 shows that the TB on day one and five have a significant correlation between the three hospitalization times. The strongest correlation is between TB day five and hospitalization time at IVZ/C4 with a high correlation (R=0.814). Also day ten shows a high correlation (R=0.719) but is not significant (R=0.069). Max TB gives a moderate correlation of R=0.533 with the total hospitalization time.

Correlations

	Hospitalisation time at IC	Hospitalization time at IVZ/C4	Total hospitalization time
Total bilirubin on day 1	.548	.465	.614
	.034	.081	.015
	15	15	15
Total bilirubin on day 5	-.026	.814	.639
	.930	.000	.014
	14	14	14
Total bilirubin on day 10	.226	.719	.543
	.626	.069	.208
	7	7	7
Max total Bilirubin value	.373	.495	.533
	.116	.031	.019
	19	19	19
Prothrombin Time on day 1	.484	-.134	.104
	.057	.620	.701
	16	16	16
Prothrombin Time on day 7	.543	.654	.676
	.105	.040	.032
	10	10	10
Prothrombin Time on day 8	.498	.690	.682
	.119	.019	.021
	11	11	11
Prothrombin Time on day 10	.948	.532	.859
	.052	.468	.141
	4	4	4
Max Prothrombin Time value	.741	.187	.452
	.000	.444	.052
	19	19	19

Figure 10: Pearson's correlations between hospitalization time, Prothrombin Time (PT) and Total Bilirubin (TB).

The PT values of day seven and eight show a significant correlation. The correlation of day one and ten are nearly significant. The highest correlation of R=0.948 is between PT on day ten and hospitalization time at the Intensive care (IC). The max PT value has a high correlation of R=0.741 with the hospitalization time at the IC. For the full table see appendices N and M.

These results show that there is a correlation between the course of the PT and the TB values and the hospitalization time. It also demonstrates that the maximum values of PT and TB have a moderate correlation to the total hospitalization time. The correlation between the maximum PT value and the hospitalization time on the IC can be explained. The PT is high right after surgery and most patients receiving a right hemihepatectomy are submitted to the IC after surgery.

The correlation of hospitalization time was analyzed for three variables; T, FLR and the ratio (T/LR)*FLR. A higher FLR is expected to correlate with a shorter hospitalization time. According to our hypothesis the ratio (T/LR)*FLR should have a negative correlation with the hospitalization time. It is expected to find a positive correlation between T and FLR. One of the significant correlations, flagged by SPSS, is pictured in a simple scatterplot as seen in figure 11. With the SPSS option 'add fit line in total' the R^2 was illustrated for the strength of the regression.

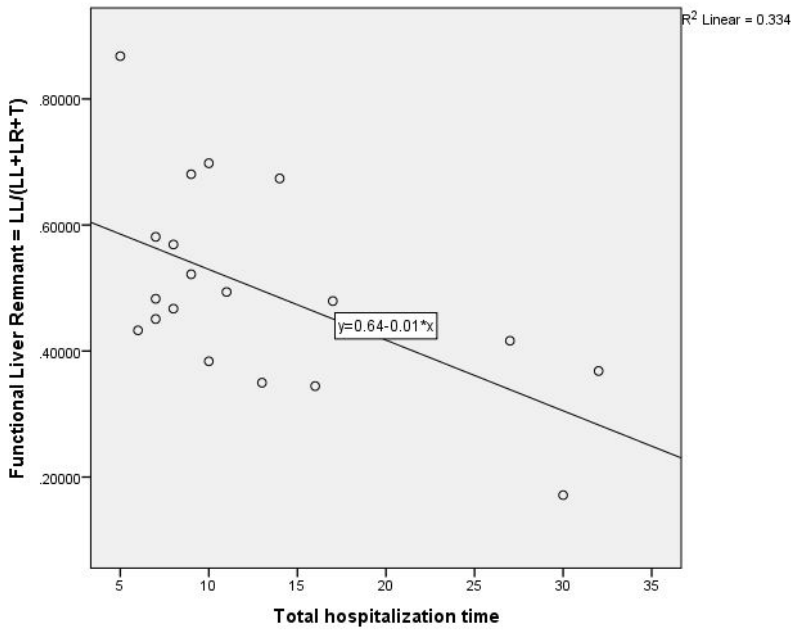


Figure 11: Scatterplot between the Functional Liver Remnant (FLR) and the total hospitalization time.

For the Pearson's Correlation table see figure 12. The moderate correlation between FLR and total hospitalization time is R=-0.578 with a significant level of p=0.010. The scatterplot of these FLR and total hospitalization time with R^2=0.334 is visible in figure 11.The ratio (T/LR)*FLR has a positive low correlation with total hospitalization of R=0.306, but

this correlation is not significant (p=0.203). Also the negative low correlation of R=-0.369 between T and FLR is not significant (p=0.120). Remarkable is the high correlation of R=.969 with significance of p=.000 between T and the ratio (T/LR)*FLR.

Correlations

		Total hospitalization time	Tumor (cm3)	Functional Liver Remnant = LL/(LL+LR+T)	Ratio T/LR * FLR
Total hospitalization time	Pearson Correlation	1	.284	-.578**	.306
	Sig. (2-tailed)		.239	.010	.203
	N	19	19	19	19
Tumor (cm3)	Pearson Correlation	.284	1	-.369	.969**
	Sig. (2-tailed)	.239		.120	.000
	N	19	19	19	19
Functional Liver Remnant = LL/(LL+LR+T)	Pearson Correlation	-.578**	-.369	1	-.311
	Sig. (2-tailed)	.010	.120		.195
	N	19	19	19	19
Ratio T/LR * FLR	Pearson Correlation	.306	.969**	-.311	1
	Sig. (2-tailed)	.203	.000	.195	
	N	19	19	19	19

**. Correlation is significant at the 0.01 level (2-tailed).

Figure 12: Pearson's correlation of the following variables: Total hospitalization time, Tumor volume (T), Functional Liver Remnant (FLR) and Ratio T/Liver Right (T/LR))*FLR.

As expected a higher FLR correlates with a shorter hospitalization time. This correlation strength is determined by 33% of the values. Contradictory to the hypothesis a negative correlation between ratio (T/LR)*FLR and the hospitalization time is not found. The expectation to find a positive correlation between T and FLR is also not found. This indicates that the size of the tumor has no effect on the size of FLR. The high correlation between T and the ratio (T/LR)*FLR indicates that the ratio is almost solely dependent on the tumor volume. The ratio needs to be reevaluated.

5.3.4 Group of eleven patients

After evaluating all previous results with our medical mentor in Groningen, some adjustments to the patient group and the ratio were made. The research group was refined by adding new exclusion criteria as described in 5.1.2. This new research population existed of eleven patients. Secondly, a new ratio was discussed. After reevaluation of the ratio it was acknowledged that the ratio should say something about the remaining liver part (LL) as well. This was missing in the previous ratio, so the ratio was adjusted to:

$$\text{Ratio} = \frac{LL}{LL+LR}$$

Ratio
In the new ratio the tumor volume is excluded because it is nonfunctional tissue. The blood values PT and BT reflect the functioning of the liver and are therefore meaningless in relation to the tumor.

Area Under the Curve
An area under the curve (AUC) was calculated for TB and PT in order to enable a valid comparison. By using AUC the course of the value of PT and TB was evaluated instead of just focusing on a specific day. The laboratory values were extrapolated in order to adjust for missing data and if day ten missed a value, this was adjusted by using the value of the first known previous day.

The AUC was calculated in MatlabR2016a (MathWorks, Massachusetts, USA) using a Riemann integral. Three AUCs were calculated:

- AUC until day five;
- AUC until day seven;
- AUC until day ten.

Method
Once more the bivariate Pearson's Correlation was performed, now between the ratio (LL/(LL+LR)) and all the AUCs of PT and TB of the eleven patients, with a significance level of $p < 0.05$.

Results
As seen in the table of figure 13 a positive moderate correlation is observed between the ratio and the different AUCs of PT. However, this correlation is not significant. A negative moderate correlation is seen in between the ratio and TB. These correlations are significant (p=0.020, p=0.031, p=0.035).

Correlations

	AUC PT till day 5	AUC PT till day 7	AUC PT till day 10	AUC TB till day 5	AUC TB till day 7	AUC TB till day 10
Ratio LL/(LL+LR)	.499	.565	.559	-.684	-.648	-.640
	.118	.070	.074	.020	.031	.034
	11	11	11	11	11	11

Figure 13: Pearson's correlation test between ratio (Liver Left/(Liver Left + Liver Right)) and all the Area Under the Curves (AUC) of Prothrombin Time (PT) and Total Bilirubin (TB).

Conclusion
As seen in the results there is a significant relationship between the ratio and the TB in this group of eleven patients. Therefore the hypothesis could be right. A positive correlation is observed between the ratio and the AUC of PT although these values are not significant they do give some insight in a possible connection between PT and the ratio. When the ratio rises (less functional liver parenchyma is lost) the PT value also rises. At first this result seems contradictory to the other result, the negative correlation between the ratio and the AUC of TB. Both PT and TB are parameters describing liver function how can the ratio have a positive correlation to the former but a negative correlation to the latter. The positive correlation with PT could be explained by the post operative increase in PT

that is observed in all patients.[26] The negative correlation between ratio and the AUC of TB is interesting, having a larger tumor thus losing less functional liver parenchyma seems to be affecting the TB in a positive manner.

5.3.5 Group of twelve patients

Another patient was added to the database as described in 5.1.3. In the final group of twelve patients a Pearson correlation between the ratio (LL/(LL+)LR) and the AUCs of day one until day five, seven and ten was performed. The group statistics were also evaluated to characterize the location and variability of the data. Lastly the ratio, the AUC of PT and the AUC of TB were correlated with the total hospitalization time. This was done to check if the patients were not only sick, but also ill. These results are visible in 6.3 Results.

In order to investigate if the group of twelve patient is normally distributed a Skewness and Kurtosis test are used. Skewness is the measure of the symmetry of distribution. Kurtosis refers to the steepness or the flatness of the distribution. Higher Kurtosis means more of the variance is the result of infrequent extreme deviations, as opposed to frequent modestly sized deviation.[27]

Properties of skewness:

- If the value for skewness is equal to zero the normal distribution is symmetric;
- If skewness is less than -1 or greater than +1, the distribution is highly skewed;
- If skewness is between -1 and -0.5 or between +0.5 and +1, the distribution is moderately skewed;
- If skewness is between -0.5 and +0.5, the distribution is approximately symmetric.

Properties of kurtosis:

- If kurtosis is exactly zero than the data is Mesokurtic;
- If kurtosis is less than zero it is called Platykurtic;
- If kurtosis is bigger than zero it is called Leptokurtic.

6 Results

6.1 Patient demographics

6.1.1 Parameters

In this study 65 patients that were hospitalized between April 2008 and December 2015 were evaluated. The flowchart in figure 14 clarifies when patients were included and excluded during the study.

In order to create homogeneity in the research population patients were excluded for the following reasons:

- Suffering from HCC(n=1);
- Suffering from gastrointestinal stromal tumor (GIST) (n=1);
- Suffering from a metastatic neuroendocrine tumor in the pancreas (n=1);
- Suffering from liver failure induced by intoxication as a result of medication use (n=1);
- Missing preoperative CT-scan of the patient's liver (n=1);
- Missing data in the electronic patient database (n=1);
- Undergoing multiple laparotomies after the hemihepatectomy right (n=1);
- Receiving previous liver surgery before undergoing a right hemihepatectomy (n=6);
- Having multiple and/or hilobar tumors (n=29);
- Tumor not visible on the CT-scan (n=2);
- Poor quality of CT-images not usable of obtaining liver volumes (n=2);
- Postoperatively suffering from a severe liver related sickness or disease. Bile leakage (n=3) and collection of fluid around the resection plane (n=2) were found.

One of the patients suffered from intro abdominal fluid collection (n=1). This could influence the health status of the patient, therefore influence the liver status and disturb other parameters.

One patient suffered from a preoperative cardiac disorder, and died within 32 days of the hemihepatectomy due an abdominal sepsis. The patient was therefore excluded from this study.

In total 53 patients were excluded from this study in the period April 2008 - December 2015. A group of twelve patients remained as the study population. An overview is available of all included and excluded patients with explanation in appendix C.

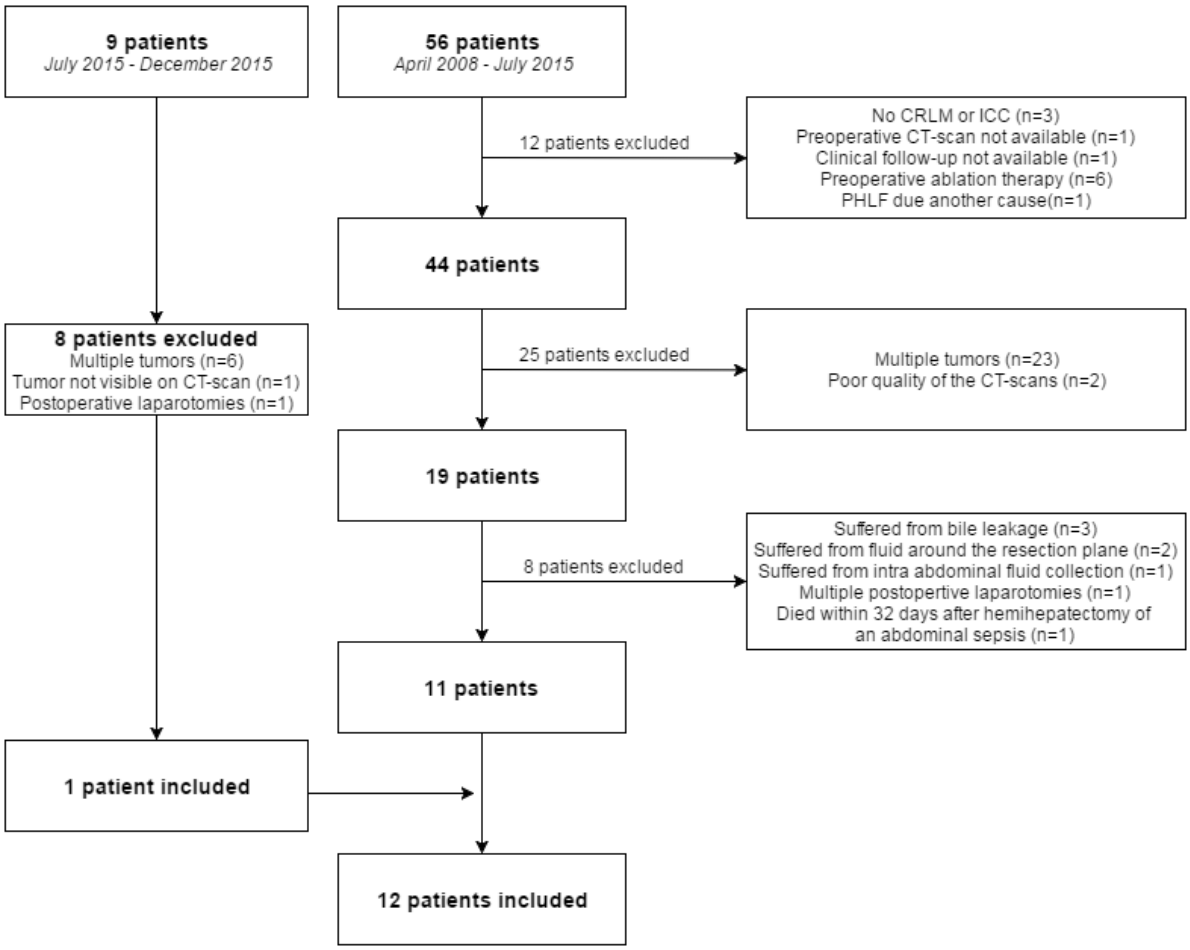


Figure 14: Flowchart of the included and excluded patients during the study.

A group of twelve patients was included, six of them male and six female. The hospitalization time of the patients varied from seven to fourteen days after surgery. A colorectal liver metastasis was presented in the right liver lobe of all patients. An ICC did not occur in the patient group. The descriptive statistics are found in table 4.

Besides the descriptive statistic the patients differ from each other in some parameters related to the patient, liver and surgery:

- 1 patient had a hemihepatectomy and hemicolectomy simultaneously;
- 1 patient had diabetes mellitus;
- 1 patient suffered from postoperative kidney failure;
- 1 patient underwent PVE;
- 1 patient was known with cholestase;
- 2 patients had neoadjuvant chemotherapy;
- 2 patients died, one 272 and the other 479 days after the surgery;
- 6 patients were known with slight hepatic steatosis.

Two patients were readmitted to the hospital within one month after surgery. One patient suffered from a pneumothorax, pulmonary embolism and biloma. The other patient suffered from wound infection.

Parameter	N	Minimum	Maximum	Mean	Std. Deviation
Age (years)	12	52	81	67.83	8.737
Weight (kg)	12	60	101	74.01	12.650
Length(cm)	12	160	192	171.65	10.114
BMI	12	21	32	25.07	3.293
Systolic BP (mmHg)	12	113	171	139.33	17.228
Diastolic BP (mmHg)	12	65	101	81.08	9.756
Blood loss (mL)	11	200	2950	1095.45	936.871
Blood products (mL)	11	0	1100	150.00	355.668

Table 4: Characteristics of the study population.

Five patients suffered from some smaller complications, such as urinary retention, chylous leak, urinary tract infection and delirium. These smaller complications are explained in appendix D.

6.1.2 Blood values

Every patient's PT and TB values from day one trough ten were collected in the database. The AUCs were calculated. The following AUCs were calculated:

- AUC of PT from day one until day five (PT 5);
- AUC of PT from day one until day seven (PT 7);
- AUC of PT from day one until day ten (PT 10);
- AUC of TB from day one until day five (TB 5);
- AUC of TB from day one until day seven (TB 7);
- AUC of TB from day one until day ten (TB 10).

The AUCs of the patient group (n=12) are summarized in table 5.

Patient number	PT 5	PT 7	PT 10	TB 5	TB 7	TB 10
2	70.6	98.6	132.5	54.0	68.0	89.0
3	60.8	86.4	119.9	88.0	119.0	165.0
4	54.0	77.8	119.9	49.0	70.5	102.5
8	46.0	72.3	106.8	66.0	116.3	169.5
9	49.6	74.2	109.0	121.5	162.5	222.5
13	51.9	75.8	110.2	49.3	70.5	98.0
18	48.3	70.0	99.9	83.5	114.5	154.5
19	49.0	69.8	100.1	121.5	156.5	198.5
20	57.0	82.4	117.8	71.5	103.3	151.0
30	48.6	70.0	102.1	53.0	73.0	103.0
42	53.1	76.5	109.9	108.5	165.5	237.5
62	44.0	60.5	105.5	175.5	237.0	314.0

Table 5: Area Under the Curve (AUC) of Prothrombin Time (PT) and Total Bilirubin (TB) until postoperative day five, seven and ten for patient group n=12.

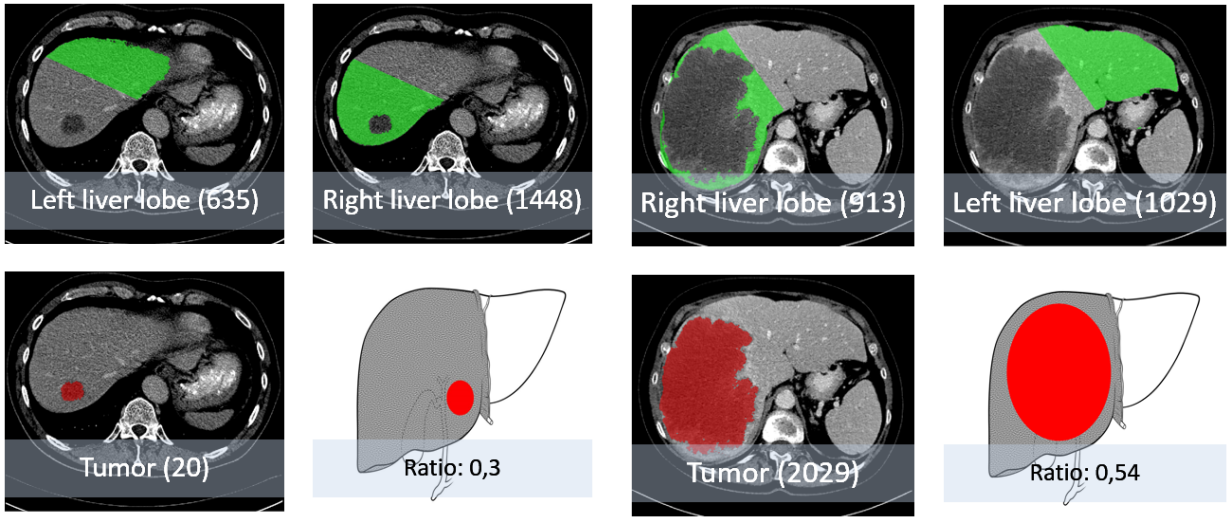
6.2 CT volumetry

The volumetric CT-based analysis of the final patient group of twelve patients resulted in the following volumes and ratios. The volumes are displayed in cubic centimeters and the ratios are dimensionless numbers describing the amount of tumorous tissue present in the resected volume in relation of the remaining liver volume.

Patient number	**LL+LR (cm^3)**	**LR (cm^3)**	**LL (cm^3)**	**T (cm^3)**	**Ratio**
2	1942	913	1029	2029	0.53
3	2400	1468	932	171	0.39
4	1770	1025	745	70	0.42
8	3823	2035	1788	25	0.47
9	2084	1448	635	20	0.30
13	2342	1358	984	103	0.42
18	3280	2231	1050	16	0.32
19	1564	1075	490	12	0.31
20	1363	960	404	92	0.30
30	2866	1789	1077	63	0.38
42	2461	1654	807	16	0.33
62	1502	944	558	2	0.37

Table 6: Volumes of the total liver, Right lobe (LR), Left lobe (LL) and the Tumor (T) are displayed in cm^3. The ratio represents the remnant liver volume (LL) divided by the volume of non-tumorous liver tissue (LL = LR + LL).

In order to visualize this ratio, Ratio = LL/(LL+LR), two patients are depicted in figure 15a and figure 15b, respectively patient nine and patient two.



(a) *The right liver lobe volume (1448cm^3), left liver lobe volume (635cm^3) and tumor volume (20cm^3) of patient nine. The ratio of patient nine(0.30) was the smallest ratio found in the research population.*

(b) *The right liver lobe volume (913cm^3), left liver lobe volume (1029cm^3) and tumor volume (2029cm^3) of patient two. The tumor volume was the largest tumor volume in the research population. The ratio of patient two (0.53) was also the largest ratio found in the research population.*

Figure 15: Visualization of the ratio.

6.3 Statistical data analysis

In this section an overview of the results of the statistic analysis from the twelve patients is given. As described in 5.3.5 a bivariate Pearson's Correlation is used to determine the strength and direction of the linear relationships between the ratio (LL/(LL+LR)) and the AUCs of PT and TB of day one until day five, seven and ten. The used confidence interval is 95% with a significant value of $p < 0.05$. Also the group statistics are examined and a correlation between the ratio and the hospitalization time was determined.

6.3.1 Ratio and AUC's

As shown in the table of figure 16, a moderate positive correlation is found between the ratio and the AUC of PT. The correlation becomes slightly stronger by adding more days in the AUC: until day five a correlation of R=0.475 (p=0.119) is found, until day seven a correlation of R=0.502 (p=0.096) and finally until day ten a correlation of R=0.557 (p=0.060). These moderate positive correlations are not significant.

On the other hand a low, but almost moderate negative correlation is found between the ratio and the AUC of TB. The correlation stays more or less the same if more days are added to the AUC: until day five a correlation of R= -0.497 (p=0.100), until day seven a correlation of R= -0.480 (p=0.114) and eventually until day ten a correlation of R=-0.489 (p=0.107). These negative correlations are not significant.

Correlations

	AUC PT till day 5	AUC PT till day 7	AUC PT till day 10	AUC TB till day 5	AUC TB till day 7	AUC TB till day 10
Ratio LL/(LL+LR)	.475	.502	.557	-.497	-.480	-.489
	.119	.096	.060	.100	.114	.107
	12	12	12	12	12	12

Figure 16: Pearson's correlation between the ratio and the Area Under the Curve (AUC) of Prothrombin Time (PT) and Total Bilirubin (TB) on day one until five, seven and ten.

6.3.2 Skewness and Kurtosis

As can been observed in figure 17 the variables Body Mass Index (BMI), blood loss and blood products are highly skewed. The variables weight and length are moderately skewed. Gender, age, systolic blood pressure and diastolic blood pressure are approximately symmetric. Gender, age, weight, length, systolic blood pressure and diastolic blood pressure are platykurtic. BMI, blood loss and bloodproducts are leptokurtic.

Statistics

		Gender	Age (years)	Weight (kg)	Lenght (cm)	Body-mass index (BMI)	Systolic blood pressure	Diastolic blood pressure	Bloodloss (ml)	Blood products (ml)
N	Valid	11	11	11	11	11	11	11	10	10
	Missing	0	0	0	0	0	0	0	1	1
Std. Deviation		.522	9.003	12.930	10.215	3.448	14.733	7.837	986.985	371.222
Variance		.273	81.055	167.174	104.355	11.887	217.073	61.418	974138.889	137805.556
Skewness		.213	-.338	.658	.515	1.099	-.164	-.377	1.534	2.277
Kurtosis		-2.444	-.388	-.268	-.713	.853	-.391	-.945	.960	4.765
Minimum		0	52	60	160	21	113	65	200	0
Maximum		1	81	101	192	32	160	89	2950	1100

Figure 17: Group statistics and normal distribution.

6.3.3 Hospitalization time

The ratio and the total hospitalization time were moderate positive correlated (R=0.423) with a significance of p= 0.171. Total hospitalization time is moderate positive correlated with the AUC of PT until day five (R=0.553, p=0.062) and day ten (R=0.554, p=0.117) and is low positive correlated with AUC of PT until day seven (R=0.477). A low negative and not significant correlation is found between the total hospitalization time and AUC of TB until five, seven and ten. The R^2 of the ratio and the total hospitalization time is only 0.179 as can be seen in appendix O.

Correlations

	Ratio LL/ (LL+LR)	AUC PT till day 5	AUC PT till day 7	AUC PT till day 10	AUC TB till day 5	AUC TB till day 7	AUC TB till day 10
Total hospitalization time	.423	.553	.477	.554	-.349	-.424	-.458
	.171	.062	.117	.062	.266	.170	.135
	12	12	12	12	12	12	12

Figure 18: Pearson's correlation between total hospitalization time and the follwoing variables: ratio: Liver Left (LL)/(LL + Liver Right (LR)), Area Under the Curve (AUC) of Prothrombin Time (PT) and Total Bilirubin (TB) of day one until day five, seven and ten.

7 Discussion

The objective of this study was to find a ratio of liver volumes that predicts the development of PHLF in patients. It was expected in the hypothesis that the size of the tumor in relation to the resected part of the liver, compared with the FLR, could predict the development of PHLF in patients. No correlation was found between the ratio, tumor volume / resection volume, and blood values of PT or TB. A new ratio of the left liver volume in relation to the total FLR was developed. This new ratio of healthy liver tissue was moderate positively correlated with PT and moderate negatively correlated with TB. These correlation were near to significance.

This study is the first to research the effect of the size of the functional part of the resected volume in relation to the FLR on PHLF. One other study, Kubota et al, investigated comparable ratios. This study showed that the resected volume, including the tumor relative to the FLR is not a predictor for PHLF. In our study similar results were found when evaluating the same ratio. Kubota et al. also looked into the ratio of the resected liver volume without the tumor in relation to the FLR, the same ratio as was used in this study. However Kubota et al. did not research the relation of that ratio to PT and TB. Kubota studied how much functional tissue could be resected before PHLF occurred. Up to 60% of the functional liver tissue can be removed. Our results are in agreement and suggest that there is a correlation between ratio and TB to be found.

7.1 Strength/Weakness

7.1.1 Including patients

Tumors other than CRLM and ICC were not included in the database. This hypothesis of this study is based on the assumption that the tumor does not contribute to the functional liver parenchyma. Thats why patients with HCC, for instance, were excluded.

The inclusion of patients was done in chronological order, starting with the most recent operation in 2015. Because of the limited time frame the inclusion ended at the patient who underwent surgery on April of 2008. Doing this may have led to a selection bias.

Tumor detection technologies have advanced greatly over the past years. Creating a scenario in which all people in the research population that have small, hard to detect tumors, received treatment in the last years. Because operating techniques have also improved patients with small, hard to detect tumors, received more advanced treatment which could in turn improve their outcome. This can be classified as a chronological bias.

The data that was obtained for this study originated from the University Medical Center Groningen (UMCG). This hospital is affiliated with the University of Groningen. The UMCG is a major hospital in the Northern Netherlands. The UMCG is one of the few hospitals to preform liver resections in the region. The hospitals that do preform these resections refer the more complicated cases to the UMCG. This may have led to a bias in the study population.

Retrospectively more exclusion criteria should have been applied. Patients who underwent VPE and neoadjuvant chemotherapy were included. Although only patients who underwent ablation therapy were excluded, VPE and chemotherapy also may have influenced on the course of the illness of the patient as well. Preoperative chemotherapy may have led to confounding.[28] PVE could have led to confounding, although PVE is minimal invasive.

Two patients lost nearly three liters of blood during the hemihepatectomy, this amount is three times higher compared to the other patients. One patient lost 2900 mL blood and received 1100 mL of donor blood by transfusion. The other one had a loss of 2950 mL and was aided with 550 mL of blood products. Blood transfusions during surgery could have an effect on the postoperative blood values of these patients with severe blood loss. Intraoperative blood loss and requirement of blood transfusion are described as possible risk factors for developing PHLF.[3] The mentioned patient should have been excluded from the study because of the severe blood loss and the effect that this might have had on the course of their illness.

For the sake of homogeneity of the research population it was decided to exclude patients who had more than one tumorous nodule. This was done by evaluating preoperative CT-scans of each of the 65 patients. Of the 65 patients 29 were excluded for this reason. The pathologist described more than one tumour in two cases of the research population (n=12). Multiple tumors were reported in patients 19 and 20 (four and six respectively). Although these these two patients were included for having one tumorous nodule based on the preoperative CT-scan. The fact that these patients were included could have compromised the homogeneity of the research population.

Alcohol consumption, smoking and genetics factors were not part of the parameters of the database. These risk factors should have been added to the database of each patient. Alcohol consumption, smoking and genetics factors may have influenced the functional liver tissue during a patient's life. Therefore these risk factors may influence the condition of the functional liver remnant after surgery. Alcohol consumption, smoking and genetics factors may have led to confounding.

The factors that are described above are improvements that could have been made. When the factors are improved in a follow-up research, they could strengthen the correlation that was found. They do not disregard our results, if all these criteria would have been applied to this study every patient would have been excluded.

7.1.2 Determining the liver volumes

The outcome of this study is based on CT based volumetry. For some patients the weight of the resection volume was reported by the pathologist and added to the database. This reported resection volume sometimes differed from the volume calculated with Matlab. These differences in weight have four possible explanations:

- According to Kubota et al. the density of liver tissue is 1 kg/dm^3. The volume and weight are distributed in a 1:1 ratio.[8] This does not automatically mean that this ratio is identical for tumorous tissue.

- Vessels containing blood were part of the liver tissue in the volumetric analysis of the CT-images. The weight of the resected tissue, measured by the pathologist, usually contains little to no blood and fluids. This could explain the discrepancy.
- Dividing the liver by using a plane created in Matlab made it possible to determine the left and right lobe in the CT-images for every patient. However this plane was straight and perpendicular to a line drawn on a single slice of the scan. It is possible that some parts of the left side of the liver were treated as being part of the left lobe of the liver and vice versa. This effect could slightly change the calculated volumes of the liver, tumor, ratio that was calculated using them and the outcome of the study.
- Another factor that may explain the difference in results is the fact that the right and left lobe separation was not done by an experienced observer. When the separation was done the results were shown to and approved by a physician. But a professional may have drawn the lines differently in the first place affecting the outcome of the volumetric calculations and the outcome of the study.

The manual adjustment of the segmentation of the CT-images was ultimately done by the investigators, therefore the results could be subjected to human error. To correct for this effect each CT-scan was manually adjusted by at least two observers. Their results were mediated, and this average was our volume. One scan was segmentend by all four observers. This test scan showed that the observers had different opinions on the boundaries of the liver and tumor. These different opinions ultimately led to a difference in volumetric outcome. It was decided that every scan should be checked twice. It would have been better if all four observers had done every scan. However this was too time-consuming for our limited time frame.

It was difficult to externally validate the CT segmentation because the data necessary was not available. It would have been better if a few CT-scans with known volumetric specifications would have been available that way differences could have been analyzed and the method could have been validated.

The gray scale images were not converted to hounds field units. This did not affect this particular research but because it lacks the standardized format of the hounds field unit reproducibility in other research could be an issue.

Most patients were referred to the UMCG trough peripheral hospitals. Usually the preoperative CT-scans are send over to the UMCG for evaluation. These hospitals do not have the same state of the art imaging technologies as the UMCG. Therefore the CT-images of these patients are of lower quality. The quality of the CT-scans influenced the determination of the volume. Older scans have bigger voxels and thicker slices. This resulted in a less accurate estimation of the volume. The quality of the CT-scans also played a part in the choice to include arteries and veins in the liver volume.

A cyst was present in some of the livers of the included patients. It was decided that this would not be part of the liver volume, because a cyst is not functioning liver parenchyma. The cyst was not part of the tumor volume either, because a cyst does not contain any cancer characteristics. Another patient had necrosis inside the tumor. This tissue was

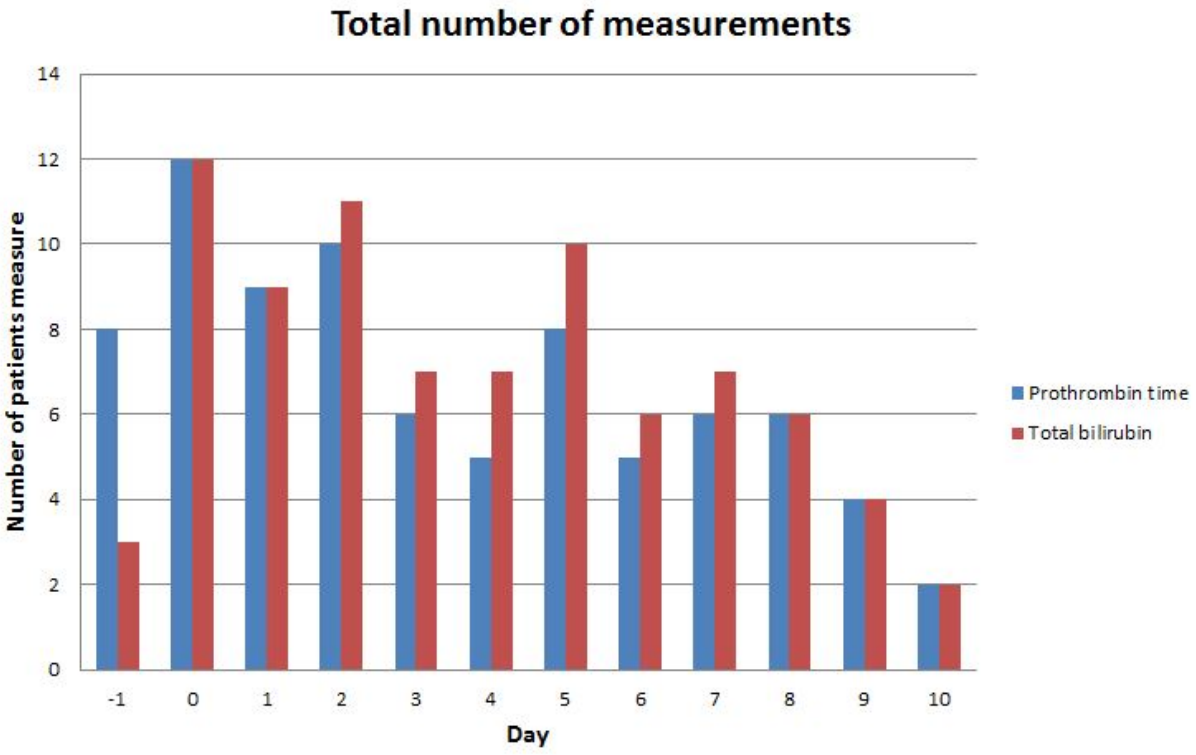


Figure 19: Total number of Prothrombin Time (PT) and Total Bilirubin (TB) measurements. As measured on day minus one to day ten.

included in the tumor volume, because of its origin.

Blood values PT and TB were investigated in relation to the different volumes. These levels were part of the data set from the UMCG. However not all patients were examined the same way during their hospitalization, this is shown in figure 19. Every patient had their PT and TB measured just before surgery. But the frequency of postoperative blood testing varied a lot (see graphic in figure 19) and is depended on hospital stay and clinical status of the patient. Due to this inconsistency obtaining a reliable picture of the progress of the blood values over time was difficult.

The different blood values were extrapolated to make analysis easier. By assuming the values would behave like they had in the available last data point information was extrapolated meaning that uncertainty was introduced.

Patients were excluded from this study if they suffered from a serious liver related complication. Due tot the fact that these complications could further influence the PT and the TB regardless of tumor size. Five of the eleven included patients suffered from smaller complications, described in appendix D. The PT and TB values of these five patients may have been influenced by these complications. And could therefore be less reliable compared to the blood levels of the seven other patients.

7.1.3 Statistical data analysis

An ideal patient group would not include any possible risk factors for developing PHLF. The patients would all be of the same gender, the same age, and there should not be any complications. These factors could all be possible confounders. The blood loss of these patients should be the same and they should not receive a blood transfusion. This is because the blood values for PT and TB might be affected by donor blood and blood loss. The heterogeneity of our patient group could cause a distorted correlation between the ratio and the blood values due to these confounders.

The sample size (n=12) is very slim. However a pilot study is only used to indicate a possible correlation and the sample size is sufficient for that purpose. Further research with a bigger sample size is needed to explore this correlation further.

During the investigation we received nine additional patients to review. From these nine patients eight were excluded and one (patient 65) was added to our research population. Preliminary statistical analysis was preformed on theses eleven patients and a statistically significant correlation was found between ratio and bilirubine. Adding the 12th patient to the research population resulted in a drop in of this correlation in significance and strenght(stat cijfers). Because the research population is fairly small (n=12) one patient could cause larger fluctuations in the results. It would be better to attain a larger research population.

7.2 Interpretation and Mechanisms

The correlation that is found between ratio (LL/(LL+LR)) and the PT is R=0.557 (p=0.060). This shows us that patients who lose relatively little functional liver parenchyma (having a higher ratio), have a higher PT value. In contrast, the correlation between the ratio (LL(LL+LR)) and the TB (R= -0.497, p=0.100) is shown to be negative meaning that a higher ratio leads to a lower TB

PT values rise in all patients after the surgery, this is to be expected because a lot of trauma was induced while operating on the patient. Because all people underwent the same operation it was to be expected that all patients experienced a similar rise it PT values.[26]

This collective rise after surgery could cause a distorted correlation, and this should be taken into consideration when forming a conclusion. These results will therefore disregarded in the clinical interpretation.

8 Conclusion

At the beginning of this study a main research question was defined. Sub-questions were composed to help answer the research question. The answers to these questions are summarized below.

What is the definition of PHLF and how do we measure this?
Various definitions of PHLF from the literature were reviewed. These different definitions were applied to our study population and used in the statistical analysis. This approach did not show any correlation and the approach was revised. PT and TB values were evaluated as continuous variables by calculating the AUC and the definitions from the literature were no longer relevant for the study.

How do we determine the volumes of the liver, tumor and resection area from CT-images?
The script that was build and used in order to segment and obtain the various volumes of the liver and tumor, was sufficient. Although manual adjustment was sometimes required the different observers did not vary more than 5% in volume determinations.

How do we shape a database based upon relevant parameters?
The relevant parameters were included to the database. These parameters were designed through a literature research. Mainly parameters that were possible risk factors of PHLF were taken into account. The database was shaped and the study population was made as homogeneous as possible. This was possible due to all the parameters that were included in the database.

How do we analyze the statistical and clinical relevance of the results?
A Pearson's correlation was used with a significance level of $p<0.05$ in order to evaluate statistical evidence for a linear relationship among the continuous variables.

The research question is: *Is it possible to predict the development PHLF in patients who receive a right hemihepatectomy by using a ratio between tumor volume, resected liver volume and the remaining liver volume acquired by CT?*

The correlations between the ratio, AUC of PT and AUC of TB are not significant. A moderate positive correlation is found between the ratio and the AUC of PT. This correlation becomes stronger when more days are added to the AUC. The correlation between the ratio and the AUC of TB is a moderate negative correlation. The number of days added to AUC did not make a big difference for this correlation.

The differences in correlations between the ratio and AUC of PT, and the ratio and AUC of TB is noteworthy. The difference can be explained by the rising of PT after trauma. The values of PT and TB together serve as a diagnostic factor for PHLF. It is odd to see that theses values have opposite correlations with the ratio. TB shows a correlation with the amount of functional liver tissue that is resected. Based upon these results it is not possible to add this ratio as a factor for predicting PHLF. However because of the small research population it is advised to conduct more research as depicted in 9.1.

9 Recommendations

9.1 Patient population

The research that was done was a retrospective study. Therefore a heterogeneous group of patients was included. This heterogeneity does not benefit the correlation that was investigated. To demonstrate a more significant correlation the a follow-up study should be a prospective study. And consider the following criteria:

- The same sex;
- All age categories;
- No complications other than PHLF;
- The same amount of blood loss;
- Patient did not receive blood transfusion;
- Patient was not preoperative treated with neoadjuvant chemotherapy;
- Patient was not treated with PVE.

The new follow-up study should consider the measurements of the blood values. PT and TB values should both be measured every day during hospitalization time.

The new follow-up study should use a bigger sample size, 50 patients should give a better insight. That way the results of the statistical analysis will be more significant and the correlations will be more meaningful.

9.2 Volumetric analysis

During the lobe division a straight line was drawn through the entire 3D array. This could be done in a better way by drawing a line through the 3D array. By placing the first point in the location where the MHV first separates from the portal vein. The second point should be placed on the point where the MHP branches.

9.3 Statistical data analysis

In this study just a Pearson's correlation test is been performed in the statistical analysis. Correlation is a coherency between two continuous variables. A causality between the two continuous variables is not automatically accepted. A proven causality makes the prediction of the dependent variable in relation with the independent variable possible. Therefore a regression analysis is required. In a next study it is necessary to evaluate the results by using a Pearson's correlation analysis and a regression analysis.

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11 Appendix

A Abbreviations

ATP	Adinoside triphosphate
ASA	America Society of Anesthesislogy
AUC	Area Under the Curve
BMI	Body Mass Index
CRLM	Colorectal Liver Metastasis
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
FLR	Future Liver Remnant
HCC	Hepatocellular Carcinoma
IC	Intensive Care
ICC	Intrahepatic Cholangiocarcinoma
INR	International Normalized Ratio
ISGLS	International Study Group of Liver Surgery
IVZ	Intensieve Verpleegkundige Zorgunit (nursing wing)
MHV	Middle Hepatic Vein
LL	Liver Left volume
LR	Liver Right volume
PHLF	Posthepatectomy Liver Failure
POD	Postoperative Day
PT	Prothrombin Time
PVE	Portal Vein Embolisation
R^2	R-squared
T	Tumor volume
TB	Total Bilirubin
UMCG	University Medical Center Groningen

B List of parameters

Category	Parameter
Patient data	Gender
	Age
	Length (cm)
	Weigth (kg)
	Body Mass Index
	Systolic Blood Pressure (mmHg)
	Diastolic Blood Pressure (mmHg)
	Preoperative Chemotherapy (neoadjuvant)
	America Society of Anesthesislogy (ASA)
	Diabetes mellitus
	Date of surgery
	Date of death
	Total hospital staying (days)
	Complications during hospital staying
Liver related data	Cirrhosis
	Fibrosis
	Cholestasis
	Steatosis
	Ischemia
	Hepatitis A, B and C
	Postoperative infection
CT data	Total liver volume
	Tumor volume
	Left liver volume
	Right liver volume
	Number of metastases according to CT-images
Operative data	Start time surgery
	End time surgery
	Which liver segments were removed
	Number og liver segments removed
	Removing middle hepatic vein
	Simultaneously colectomy
	Blood loss
	Blood product
	Resection weight according to pathologist
	Resection size according to pathologist
	Tumor size according to pathologist
	Portal Vein Embolisation
	Rehospitalization of patient within a month
Blood values	Prothrombin time
	Total bilirubin

C Included and excluded patients

Patient number	Included/Excluded
1	Excluded, because of multiple tumors.
2	Included.
3	Included.
4	Included.
5	Excluded, because this patient suffered from fluid collection around the resection plane.
6	Excluded, because this patient suffered from hepatocellular carcinoma.
7	Excluded, because this patient suffered from an intra-abdominal fluid collection.
8	Included.
9	Included.
10	Excluded, because the tumor was not visible on the CT-images.
11	Excluded, because of multiple tumors.
12	Excluded, because of multiple tumors.
13	Included.
14	Excluded, because of multiple tumors.
15	Excluded, because of multiple tumors.
16	Excluded, because this patient was earlier treated with ablation therapy before the right hemihepatectomy.
17	Excluded, because of multiple tumors.
18	Included.
19	Included.
20	Included.
21	Excluded, because this patient suffered from gastrointestinal stromal tumor.
22	Excluded, because this patient suffered from a metastatic from a neuroendocrine tumor in the pancreas.
23	Excluded, because of multiple tumors.
24	Excluded, because this patient died within 32 of an abdominal sepsis.
25	Excluded, because of multiple tumors.
26	Excluded, because this patient suffered from PHLF induced by intoxication as a result of medication use.
27	Excluded, because this patient was earlier treated with ablation therapy before the right hemihepatectomy.
28	Excluded, because this patient was earlier treated with ablation therapy before the right hemihepatectomy.
29	Excluded, because of multiple tumors.
30	Included.
31	Excluded, because of multiple tumors.
32	Excluded, because of multiple tumors.

33	Excluded, because of multiple tumors.
34	Excluded, because of multiple tumors.
35	Excluded, because this patient was earlier treated with ablation therapy before the right hemihepatectomy.
36	Excluded, because this patient suffered from bile leakage.
37	Excluded, because of multiple tumors.
38	Excluded, because of multiple tumors.
39	Excluded, because this patient suffered from bile leakage.
40	Excluded, because this patient suffered from fluid collection around the resection plane.
41	Excluded, because of multiple tumors.
42	Included.
43	Excluded, because of multiple tumors.
44	Excluded, because of multiple tumo53rs.
45	Excluded, because this patient was earlier treated with ablation therapy before the right hemihepatectomy.
46	Excluded, because not all the needed patient parameters were available.
47	Excluded, because a preoperative CT-scan was not available.
48	Excluded, because this patient was earlier treated with ablation therapy before the right hemihepatectomy.
49	Excluded, because of multiple tumors.
50	Excluded, because of multiple tumors.
51	Excluded, because of poor quality of the CT-images.
52	Excluded, because of multiple tumors.
53	Excluded, because of multiple tumors.
54	Excluded, because of poor quality of the CT-images.
55	Excluded, because this patient suffered from bile leakage.
56	Excluded, because of multiple tumors.
57	Excluded, because of multiple tumors.
58	Excluded, because this patient had two laparotomies after the hemihepatectomy right.
59	Excluded, because of multiple tumors.
60	Excluded, because the tumor was not visible on the CT-images.
61	Excluded, because of multiple tumors.
62	Included.
63	Excluded, because of multiple tumors.
64	Excluded, because of multiple tumors.
65	Excluded, because of multiple tumors.

D Explanation smaller complications

Patient number	Smaller complications	Explanation
3, 18	Urinary retention	The inability to completely empty the bladder.
13	Chylous leak	Leakage of lymphatic fluid from the lymphatic vessels.
13, 42	Urinary tract infection	Infection of of the lower (the urethra or urinary bladder) or higher urinary tract (ureter or kidney).
20	Delirium	This is a acute confusional state. This clinical syndrome involves cognitive deficits and psychotic features such as hallucinations and delusions.

E Reading DICOM files

```
%start with clean slate
clear       %no variables
close all   %no figures
clc         %empty command window

patientnumber ='test'; %insert patiëntnumber here
firstfile = 10000000 %Fill in the filename of the first file of the DICOM data set
lastfile = 10003300 %Fill in the filename of the last file of the DICOM data set
```

```
firstfile =

    10000000


lastfile =

    10003300
```

Turning files into 3D array

```
%-----------------------------------------------------------------------
fnum = firstfile:11:lastfile;

%first filename in series
fname = num2str(fnum(1));

%examine file
info = dicominfo(fname)

%extract size info from metadata (nobkpt)
voxel_size = [info.PixelSpacing; info.SliceThickness]'

%read slice images; populate XYZ matrix
hWaitBar = waitbar(0,'Reading DICOM files');
for i=length(fnum):-1:1
  fname = [num2str(fnum(i))];
  CTdata(:,:,i) = uint16(dicomread(fname));
  waitbar((length(fnum)-i)/length(fnum))
end

delete(hWaitBar)
whos CTdata %Check if CTdata contains data
```

```
Error using dicominfo>getFileDetails (line 526)
File "10000000" not found.

Error in dicominfo (line 52)
    fileDetails = getFileDetails(filename);

Error in Reading_DICOMexample (line 18)
info = dicominfo(fname)
```

Visualization single image

```
%-----------------------------------------------------------------------
%Display the image using imtool
i = 1;  %i is the slice you want to view
g = [1 1500];
im = squeeze(CTdata(:,:,i));
imtool(im,g) %Show im with grayscale g, adjust acorrdingly the maximum pixel value ir
```

Visualization by scrolling

```
close all
imtool CLOSE ALL
g = [xxx xxxx];  %g is the pixel range you want to display use prior image as a refer
imtool3D(CTdata,[],[],g);
```

Only display slices in which the liver is present

```
close all
imtool CLOSE ALL
UL= xx; %define the slice containing the upperlimit of the liver (find it using the p
LL= xx;  %define the slice containing the lowerlimit of the liver (find it using the

CTdatacrop=CTdata(:,:,[LL:UL]);

imtool3D(CTdatacrop,[],[],g); %check if the liver is inside the specified bounds
```

Saving the file in the patient specific folder (patientnumber has to be specified @ line 7)

```
%Change according to your drive location
close all
folder1         = 'D:';
folder2         = 'Server';
folder3         = 'example user';
folder4         = 'example location';
patientfolder   = ['pat.' patientnumber];
```

```
%Minder mappen? ook weghalen uit F1
F1 = fullfile(folder1,folder2,folder3,folder4,'MDO','5.Iedereen','Data','Pat.folders
F2 = fullfile(folder1,folder2,folder3,folder4,'MDO','5.Iedereen','Data','Pat.folders

save(F1, 'CTdata', '-mat')
save(F2, 'firstfile','CTdatacrop','g', '-mat')
```

F Segmentation

```
%start with clean slate
clear       % No variables
close all   % No figures
clc         % Empty command window
```

Labeling the patiënt

```
patientnumber = 'example'; % Insert patientnumber

load(['CTdatacrop' patientnumber '.mat']);
```

```
Error using load
Unable to read file 'CTdatacropexample.mat'. No such file or directory.

Error in Segmentatieexample (line 9)
load(['CTdatacrop' patientnumber '.mat']);
```

Show histogram of the cropped image

```
historange = CTdatacrop > g(1) & CTdatacrop < g(2); % Use the bounds specified while
histogram(CTdatacrop(historange));
```

Segmentation of the liver trough thresholding

```
LBL = xxxx; % Enter upper and lower bounds based on Histogram
UBL = xxxx;

BWCTdata = (CTdatacrop>LBL) & (CTdatacrop<UBL);
close all
imtool3D(BWCTdata,[],[],g); % Check if the liver is mostly white and other tissues ar
                            % If this is not the case play around with the bounds to
```

Segment the liver

```
se1=strel('disk',1); % Adjust the strel sizes en classes for the best effect (disk/di
se2=strel('disk',1);

BW1 = imopen(BWCTdata,se1);
BW2 = bwlabeln(BW1,26); % If the liver connect to diffrent tissue or doenst connect t
stats = regionprops(BW2,'Area');
S = [stats.Area];
biggest = find (S==max(S));
BW3 = ismember(BW2, biggest);
```

```
BW4 = imdilate(BW3,se2);
CTSegmentedLiverBinary = imerode(BW4,se2);

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedLiverBinary);% Check if the Segmentation is valid if not char
```

If the hearth is in the segmentation try removing (part of) it with this section

If the hearth is not connected to the liver in HLSlice = [1:1];

```
HLSlice = [1:1];
HBW1 = CTSegmentedLiverBinary(:,:,HLSlice);
HBW2 = bwlabeln(HBW1,18);
stats = regionprops(HBW2,'Area');
S = [stats.Area];
biggest = find (S==max(S)); % If the hearth is the biggest use (S~=max(S)), if the li
HBW3 = ismember(HBW2, biggest);

HBW4 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),((size(CTdatacrop,3))-(size(HLS
CTSegmentedLiverBinarynew = cat(3,HBW3,HBW4).*CTSegmentedLiverBinary;

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedLiverBinarynew) % Check if the heart is removed, if not lower
```

Remove first section in the middle

```
ML1Slice = [1:1]; % If, for instance, the kidneys are connected in some, but not all,
HBW1 = CTSegmentedLiverBinarynew(:,:,ML1Slice);
HBW2 = bwlabeln(HBW1,18);
stats = regionprops(HBW2,'Area');
S = [stats.Area];
biggest = find (S==max(S));
HBW3 = ismember(HBW2, biggest);
HBW4 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(ML1Slice(1)-1));
HBW5 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(size(CTdatacrop,3))-ML1Slice(e
CTSegmentedLiverBinarynew = cat(3,HBW4,HBW3,HBW5).*CTSegmentedLiverBinarynew;

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedLiverBinarynew)
```

Remove second section in the middle

```
ML2Slice = [1:1];
HBW1 = CTSegmentedLiverBinarynew(:,:,ML2Slice);
HBW2 = bwlabeln(HBW1,18);
```

```
stats = regionprops(HBW2,'Area');
S = [stats.Area];
biggest = find (S==max(S));
HBW3 = ismember(HBW2, biggest);
HBW4 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(ML2Slice(1)-1));
HBW5 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(size(CTdatacrop,3))-ML2Slice(e
CTSegmentedLiverBinarynew = cat(3,HBW4,HBW3,HBW5).*CTSegmentedLiverBinarynew;

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedLiverBinarynew)
```

Remove third section in the middle

```
ML3Slice = [1:1];
HBW1 = CTSegmentedLiverBinarynew(:,:,ML3Slice);
HBW2 = bwlabeln(HBW1,18);
stats = regionprops(HBW2,'Area');
S = [stats.Area];
biggest = find (S==max(S));
HBW3 = ismember(HBW2, biggest);
HBW4 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(ML3Slice(1)-1));
HBW5 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(size(CTdatacrop,3))-ML3Slice(e
CTSegmentedLiverBinarynew = cat(3,HBW4,HBW3,HBW5).*CTSegmentedLiverBinarynew;

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedLiverBinarynew)
```

Remove section at the bottem

```
close all
LLSlice = [1:(size(CTdatacrop,3))];
HBW1 = CTSegmentedLiverBinarynew(:,:,LLSlice);
HBW2 = bwlabeln(HBW1,18);
stats = regionprops(HBW2,'Area');
S = [stats.Area];
biggest = find (S==max(S));
HBW3 = ismember(HBW2, biggest);
HBW4 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(LLSlice(1)-1));
HBW5 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(size(CTdatacrop,3))-LLSlice(en
CTSegmentedLiverBinarynew = cat(3,HBW4,HBW3,HBW5).*CTSegmentedLiverBinarynew;

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedLiverBinarynew) % Check the final result
```

```
%Segment the Tumor
% Find the Tumor and define the rough edges in x coordinates (line 124)y
% coordinates (line 125) and z coordinates (line 126).
close all
imtool3D(CTdatacrop, [],[],g);
```

Fill in the coördinates edges

```
TumorX = [xxx:xxx];
TumorY = [xxx:xxx];
TumorZ = [xxx:xxx];
TumorMask = zeros(size(CTdatacrop,1),size(CTdatacrop,2),size(CTdatacrop,3));
TumorMask(TumorY,TumorX,TumorZ) = 1;
TumorRough = CTdatacrop.*uint16(TumorMask);
```

Show histogram of TumorRough

```
close all
historange = TumorRough > g(1) & TumorRough < LBL; % By default the bounds are specif
histogram(TumorRough(historange));
```

Segmentation of the tumor trough thresholding

```
LBT = xxxx; %Enter the lower bound based on Histogram Of Tumor
UBT = xxxx;

BWTumorRough = (TumorRough>LBT) & (TumorRough<UBT);
imtool3D(BWTumorRough,[],[],g); % Check if the tumor is mostly white and the remainir
```

Segment the tumor

```
close all
se3=strel('disk',1); % Adjust the strel sizes en classes for the best effect (disk/di
se4=strel('disk',1);

BW1 = imopen(BWTumorRough,se3);
BW2 = bwlabeln(BW1,18);
stats = regionprops(BW2,'Area');
S = [stats.Area];
biggest = find (S==max(S));
BW3 = ismember(BW2, biggest);
BW4 = imdilate(BW3,se4);
CTSegmentedTumorBinary = imerode(BW4,se4);
```

```
tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedTumorBinary); %Check if the segmentation of the tumor is vali
```

Remove higher section

```
HTSlice = [1:1]; % Usually the tumor is not plagued by interconectivity with other ti
HBW1 = CTSegmentedTumorBinary(:,:,HTSlice);
HBW2 = bwlabeln(HBW1,26);
stats = regionprops(HBW2,'Area');
S = [stats.Area];
biggest = find (S==max(S));
HBW3 = ismember(HBW2, biggest);

HBW4 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),((size(CTdatacrop,3))-(size(HTS
CTSegmentedTumorBinarynew = cat(3,HBW3,HBW4).*CTSegmentedTumorBinary;

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedTumorBinarynew)
```

Remove first section in the middle if needed

```
MT1Slice = [1:1];
HBW1 = CTSegmentedTumorBinarynew(:,:,MT1Slice);
HBW2 = bwlabeln(HBW1,18);
stats = regionprops(HBW2,'Area');
S = [stats.Area];
biggest = find (S==max(S));
HBW3 = ismember(HBW2, biggest);
HBW4 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(MT1Slice(1)-1));
HBW5 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(size(CTdatacrop,3))-MT1Slice(e
CTSegmentedTumorBinarynew = cat(3,HBW4,HBW3,HBW5).*CTSegmentedTumorBinarynew;

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedTumorBinarynew)
```

Remove second section in the middle if needed

```
MT2Slice = [1:1];
HBW1 = CTSegmentedTumorBinarynew(:,:,MT2Slice);
HBW2 = bwlabeln(HBW1,18);
stats = regionprops(HBW2,'Area');
S = [stats.Area];
biggest = find (S==max(S));
HBW3 = ismember(HBW2, biggest);
HBW4 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(MT2Slice(1)-1));
```

```
HBW5 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(size(CTdatacrop,3))-MT2Slice(e
CTSegmentedTumorBinarynew = cat(3,HBW4,HBW3,HBW5).*CTSegmentedTumorBinarynew;

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedTumorBinarynew)
```

Remove third section in the middle if needed

```
MT3Slice = [1:1];
HBW1 = CTSegmentedTumorBinarynew(:,:,MT3Slice);
HBW2 = bwlabeln(HBW1,18);
stats = regionprops(HBW2,'Area');
S = [stats.Area];
biggest = find (S==max(S));
HBW3 = ismember(HBW2, biggest);
HBW4 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(MT3Slice(1)-1));
HBW5 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(size(CTdatacrop,3))-MT3Slice(e
CTSegmentedTumorBinarynew = cat(3,HBW4,HBW3,HBW5).*CTSegmentedTumorBinarynew;

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedTumorBinarynew)
```

Remove section at the bottem

```
close all
LTSlice = [1:(size(CTdatacrop,3))];
HBW1 = CTSegmentedTumorBinarynew(:,:,LTSlice);
HBW2 = bwlabeln(HBW1,18);
stats = regionprops(HBW2,'Area');
S = [stats.Area];
biggest = find (S==max(S));
HBW3 = ismember(HBW2, biggest);
HBW4 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(LTSlice(1)-1));
HBW5 = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)),(size(CTdatacrop,3))-LTSlice(en
CTSegmentedTumorBinarynew = cat(3,HBW4,HBW3,HBW5).*CTSegmentedTumorBinarynew;

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedTumorBinarynew)
```

Saving the file in the patient specific folder (patientnumber has to be specified @ line 7)

```
%Change according to your drive location
close all
folder1         = 'D:';
folder2         = 'Server';
```

```
folder3         = 'example user';
folder4         = 'example location';
patientfolder   = ['pat.' patientnumber];

F1 = fullfile(folder1,folder2,folder3,folder4,'MDO','5.Iedereen','Data','Pat.folders
save(F1, 'CTSegmentedLiverBinarynew','CTSegmentedTumorBinarynew', '-mat')

F3 = fullfile(folder1,folder2,folder3,folder4,folder5,folder6,'MDO','5.Iedereen','Dat
save(F3,'g','LBL','UBL','UBT','LBT','TumorX','TumorY','TumorZ','HLSlice','ML1Slice',
% Store the variables used in the segmentation ir oder to easily recreate
% the process should it be necessary
```

G Finalizing segmentation

```
%start with clean slate
clear       % No variables
close all   % No figures
clc         % Empty command window
```

Labeling the patiënt

```
patientnumber = 'example'; % Insert patientnumber

Observer = 'example'; % Your name

load(['CTdatacrop' patientnumber '.mat']);
load(['CTMask' patientnumber '.mat']);
```

```
Error using load
Unable to read file 'CTdatacropexample.mat'. No such file or directory.

Error in Finalizingsegmentationexample (line 11)
load(['CTdatacrop' patientnumber '.mat']);
```

Finalizing the segmented liver

```
tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedLiverBinarynew); %Fill in the tumor and the liver!

CTSegmentedLiverBinarynew = getMask(tool);
tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedLiverBinarynew); %check if the result and touch up if needed.

CTLiverMaskTemp = getMask(tool);
```

Finalizing the segmented tumor

```
tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedTumorBinarynew); %Fill in the tumor only!

CTSegmentedTumorBinarynew = getMask(tool);
tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTSegmentedTumorBinarynew); %check if the result and touch up if needed.

CTTumorMaskFinal = getMask(tool);
CTLiverMaskFinal = CTLiverMaskTemp - CTTumorMaskFinal;
```

Saving the file in the patient specific folder (patientnumber has to be specified @ line 7)

```
%Change according to your drive location
close all
folder1         = 'D:';
folder2         = 'Server';
folder3         = 'example user';
folder4         = 'example location';
patientfolder   = ['pat.' patientnumber];

F1 = fullfile(folder1,folder2,folder3,folder4,'MDO','5.Iedereen','Data','Pat.folders
save(F1, 'CTLiverMaskFinal','CTTumorMaskFinal', '-mat')
```

H Lobe division

```
%start with clean slate
clear       % No variables
close all   % No figures
clc         % Empty command window
```

Labeling the patiënt

```
Patientnumber = 'example'; % Insert patientnumber

Observer = 'example'; % First letter of your name

load(['CTdatacrop' Patientnumber '.mat']);
load(['CTMaskFinal' Patientnumber Observer '.mat']);
```

```
Error using load
Unable to read file 'CTdatacropexample.mat'. No such file or directory.

Error in Lobedivisionexample (line 11)
load(['CTdatacrop' Patientnumber '.mat']);
```

Dividing the Liver in Left and Right

```
close all
imtool3D(CTdatacrop,[],[],g); % Search for the Right hepatic vein that divides the ri

slice =xx; % Fill in the slicenumber
figure,imshow((CTdatacrop(:,:,slice)),g);

p1 = [xxx xxx]; % Define two outerpoints of a line trough the right hepatic vein (Y,X
p2 = [xxx xxx];

Mask = zeros((size(CTdatacrop,1)),(size(CTdatacrop,2)));
[ind label] = drawline(p1,p2,[(size(CTdatacrop,2)) (size(CTdatacrop,2))]);
Mask(ind) = label;
figure,imshow(Mask,[0 1]);

se = strel('disk',1);
Mask1 = imdilate(Mask,se);
TumorMask = ones((size(CTdatacrop,1)),(size(CTdatacrop,2)));
Mask2 = (Mask1 - TumorMask);

Mask3 = bwlabel(Mask2,8);
stats = regionprops(Mask1,'Area');
S = [stats.Area];
```

```
smallest = find (S==min(S));
MaskLL1 = ismember(Mask3, smallest);
MaskRL1 = ~MaskLL1;

for i = 1:(size(CTdatacrop,3));
MaskRL(:,:,i) = MaskRL1;
end

for i = 1:(size(CTdatacrop,3));
MaskLL(:,:,i) = MaskLL1;
end

CTsegmentedRightBinary=CTLiverMaskFinal.*MaskRL;
CTsegmentedLeftBinary =CTLiverMaskFinal.*MaskLL;

CTsegmentedRight=CTdatacrop.*uint16(CTsegmentedRightBinary);
CTsegmentedLeft=CTdatacrop.*uint16(CTsegmentedLeftBinary);
```

Check if the division of lobes is succesfull

```
close all
imtool3D(CTsegmentedRight,[],[],g)% If the images are swapped (FIG1 should be right)
imtool3D(CTsegmentedLeft,[],[],g)
```

Saving the file in the patient specific folder (patientnumber has to be specified @ line 7)

```
%Change according to your drive location
close all
folder1         = 'D:';
folder2         = 'Server';
folder3         = 'example user';
folder4         = 'example location';
patientfolder   = ['pat.' patientnumber];

F1 = fullfile(folder1,folder2,folder3,folder4,'MDO','5.Iedereen','Data','Pat.folders
save(F1, 'CTsegmentedRightBinary', 'CTsegmentedLeftBinary','CTsegmentedRight','CTsegm
F2 = fullfile(folder1,folder2,folder3,folder4,'MDO','5.Iedereen','Data','Pat.folders
save(F2,'slice','p1','p2','-mat')
```

I Volumetric analysis

```
%start with clean slate
clear       % No variables
close all   % No figures
clc         % Empty command window
```

Volumetric calculation

```
patientnumber = 'example'% Insert patientnumber
Observer = 'example'; % First letter of your name

load(['CTMaskFinal' patientnumber Observer '.mat']);
load(['Lobedivision' patientnumber Observer '.mat']);
load(['CTdatacrop' patientnumber '.mat']);
```

```
patientnumber =

example



Error using load
Unable to read file 'CTMaskFinalexampleexample.mat'. No such file or directory.

Error in Volumetricanalysisexample (line 11)
load(['CTMaskFinal' patientnumber Observer '.mat']);
```

Calculate voxel volume

```
info = dicominfo(firstfile);
A = info.SliceThickness;
B = info.PixelSpacing;
Volume_Voxel = A.*B(1).*B(2)
```

Count all elements not equal to zero

```
clc
Right = (nnz(CTsegmentedRightBinary).*Volume_Voxel/1000); % Divide by 1000 to convert
Left = (nnz(CTsegmentedLeftBinary).*Volume_Voxel/1000);
Tumor = (nnz(CTTumorMaskFinal).*Volume_Voxel/1000);
Liver = (nnz(CTLiverMaskFinal).*Volume_Voxel/1000);

Volume_Liver = [num2str(Liver) 'cm^3'] % Display the volume of each analysed element
Volume_Right = [num2str(Right) 'cm^3']
Volume_Left = [num2str(Left) 'cm^3']
Volume_Tumor = [num2str(Tumor) 'cm^3']
```

Ratio bepalen

```
clc
Ratio = [num2str(Left/Liver) ' Percent']        % Calculate the Ratio used in our stu
FLR = [num2str(Left./(Liver+Tumor)) ' percent'] % Calculate the FLR
```

Saving the file in the patient specific folder (patientnumber has to be specified @ line 8)

Change according to your drive location

```
close all
folder1         = 'D:';
folder2         = 'Server';
folder3         = 'example user';
folder4         = 'example location';
patientfolder   = ['pat.' patientnumber];

F1 = fullfile(folder1,folder2,folder3,folder4,'MDO','5.Iedereen','Data','Pat.folders

save(F1,'Volume_Liver','Volume_Right','Volume_Left','Volume_Tumor','Ratio','FLR', '-m
```

J Show results

```
clear all
close all
clc

Patientnumber = 'example'; % Insert patiënt number (format: 00xx)
Observer = 'example'; % First letter of your name

load(['CTdatacrop' Patientnumber '.mat']);
load(['CTMaskFinal' Patientnumber Observer '.mat']);
load(['Lobedivision' Patientnumber Observer '.mat']);
load(['LobedivisionPoints' Patientnumber Observer '.mat']);
load(['Volumes' Patientnumber Observer '.mat']);


Error using load
Unable to read file 'CTdatacropexample.mat'. No such file or directory.

Error in ShowResultsexample (line 9)
load(['CTdatacrop' Patientnumber '.mat']);
```

Display segmented Liver

```
close all
tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTLiverMaskFinal);
setAlpha(tool,.5);
setMaskColor(tool,[0 1 0])
Volume_Liver
```

Display segmented Tumor

```
close all
clc
tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTTumorMaskFinal);
setAlpha(tool,.5);
Volume_Tumor
```

Display dividing line between right and left

```
close all
Mask = zeros((size(CTdatacrop,1)),(size(CTdatacrop,2)));
[ind label] = drawline(p1,p2,[(size(CTdatacrop,2)) (size(CTdatacrop,2))]);
Mask(ind) = label;
```

```
se = strel('disk',3);
Mask1 = imdilate(Mask,se);

for i = 1:(size(CTdatacrop,3));
MaskDiv(:,:,i) = Mask1;
end

tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,MaskDiv);
setAlpha(tool,.5);
setMaskColor(tool,[0 .5 1])
```

Display Left Liver

```
close all
tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTsegmentedLeftBinary);
setAlpha(tool,.5);
setMaskColor(tool,[0 1 0])
Volume_Left
```

Display Right Liver

```
close all
tool = imtool3D(CTdatacrop,[],[],g);
setMask(tool,CTsegmentedRightBinary);
setAlpha(tool,.5);
setMaskColor(tool,[0 1 0])
Volume_Right
```

K Pearson's correlation: first ratio, FLR and PT values

Correlations

	Ratio T/LR * FLR	Functional Liver Remnant = LL/(LL+LR+T)
Prothrombin Time week for surgery	.524 .080 12	.303 .339 12
Prothrombin Time before surgery	.647 .007 16	-.353 .180 16
Prothrombin Time on day 1	.836 .000 16	-.075 .783 16
Prothrombin Time on day 2	.444 .074 17	.251 .332 17
Prothrombin Time on day 3	.459 .133 12	.079 .807 12
Prothrombin Time on day 4	.362 .248 12	.239 .454 12
Prothrombin Time on day 5	.661 .019 12	-.102 .753 12
Prothrombin Time on day 6	.120 .741 10	.322 .364 10
Prothrombin Time on day 7	.509 .133 10	-.187 .604 10
Prothrombin Time on day 8	-.091 .789 11	-.197 .561 11
Prothrombin Time on day 9	-.260 .535 8	-.310 .454 8
Prothrombin Time on day 10	.846 .154 4	-.650 .350 4
Max Prothrombin Time value	.537 .018 19	-.174 .476 19

Figure 20

L Pearson's correlation: first ratio, FLR and TB values

Correlations

	Ratio T/LR * FLR	Functional Liver Remnant = LL/(LL+LR+T)
Total bilirubin week for surgery	.095 .858 6	.085 .873 6
Total bilirubin before surgery	.153 .587 15	-.116 .680 15
Total bilirubin on day 1	.158 .573 15	-.338 .218 15
Total bilirubin on day 2	-.096 .706 18	-.111 .662 18
Total bilirubin on day 3	-.273 .367 13	-.285 .345 13
Total bilirubin on day 4	-.340 .235 14	-.126 .668 14
Total bilirubin on day 5	-.247 .394 14	-.299 .298 14
Total bilirubin on day 6	-.369 .264 11	-.172 .614 11
Total bilirubin on day 7	-.320 .338 11	.093 .785 11
Total bilirubin on day 8	-.162 .614 12	-.165 .609 12
Total bilirubin on day 9	-.491 .180 9	.138 .723 9
Total bilirubin on day 10	-.226 .626 7	-.800 .031 7
Max total Bilirubin value	-.130 .597 19	-.262 .278 19

Figure 21

M Pearson's correlation: hospitalization time and PT values

Correlations

	Hospitalization time at IC	Hospitalization time at IVZ/C4	Total hospitalization time
Prothrombin Time week for surgery	.154	-.665	-.530
	.632	.018	.076
	12	12	12
Prothrombin Time before surgery	.673	.001	.157
	.004	.998	.560
	16	16	16
Prothrombin Time on day 1	.484	-.134	.104
	.057	.620	.701
	16	16	16
Prothrombin Time on day 2	.147	-.321	-.180
	.572	.210	.490
	17	17	17
Prothrombin Time on day 3	.256	-.186	-.027
	.422	.563	.933
	12	12	12
Prothrombin Time on day 4	.021	-.520	-.390
	.948	.083	.211
	12	12	12
Prothrombin Time on day 5	.318	.031	.176
	.314	.923	.584
	12	12	12
Prothrombin Time on day 6	.198	-.304	-.074
	.583	.394	.840
	10	10	10
Prothrombin Time on day 7	.543	.654	.676
	.105	.040	.032
	10	10	10
Prothrombin Time on day 8	.498	.690	.682
	.119	.019	.021
	11	11	11
Prothrombin Time on day 9	.433	.666	.661
	.284	.071	.074
	8	8	8
Prothrombin Time on day 10	.948	.532	.859
	.052	.468	.141
	4	4	4
Max Prothrombin Time value	.741	.187	.452
	.000	.444	.052
	19	19	19

Figure 22

N Pearson's correlation: hospitalization time and TB values

Correlations

	Hospitalization time at IC	Hospitalization time at IVZ/C4	Total hospitalization time
Total bilirubin week for surgery	-.139	-.327	-.248
	.793	.528	.635
	6	6	6
Total bilirubin before surgery	.205	-.152	-.100
	.463	.589	.724
	15	15	15
Total bilirubin on day 1	.548	.465	.614
	.034	.081	.015
	15	15	15
Total bilirubin on day 2	.348	.359	.422
	.157	.143	.081
	18	18	18
Total bilirubin on day 3	.196	.281	.298
	.521	.353	.322
	13	13	13
Total bilirubin on day 4	-.048	.338	.239
	.871	.237	.411
	14	14	14
Total bilirubin on day 5	-.026	.814	.639
	.930	.000	.014
	14	14	14
Total bilirubin on day 6	-.114	.264	.200
	.738	.433	.556
	11	11	11
Total bilirubin on day 7	-.034	.353	.307
	.921	.287	.358
	11	11	11
Total bilirubin on day 8	.358	.448	.499
	.253	.144	.099
	12	12	12
Total bilirubin on day 9	-.048	.216	.148
	.902	.577	.704
	9	9	9
Total bilirubin on day 10	.226	.719	.543
	.626	.069	.208
	7	7	7
Max total Bilirubin value	.373	.495	.533
	.116	.031	.019
	19	19	19

Figure 23

O Scatterplot of the ratio and the total hospitalization time

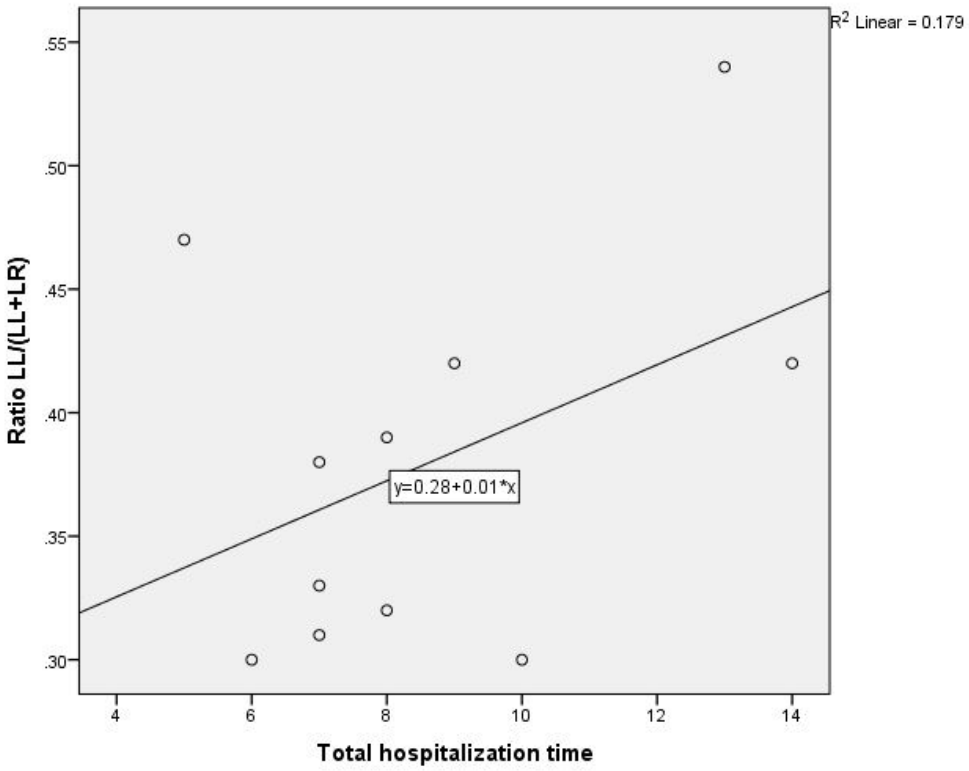

Figure 24