Combinations of liver lobe and spleen volumes obtained on magnetic resonance imaging to predict esophagogastroduodenal variceal bleeding in hepatitis B-related cirrhotic patients
A prospective cohort study

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Abstract
To evaluate whether combinations of liver lobe and spleen volumes obtained on magnetic resonance imaging (MRI) could predict esophagogastroduodenal variceal bleeding (EVb) in hepatitis B-related cirrhotic patients. Ninety-six consecutive patients with hepatitis B-related cirrhosis underwent upper abdominal contrast-enhanced MRI within 1 week after initial hospitalization, and grouped based on outcomes of EVB during the 2 years’ follow-up after being discharged. Total liver volume (TLV), spleen volume (SV) and 4 liver lobe volumes including right lobe volume (RV), left medial lobe volume (LMV), left lateral lobe volume (LLV), and caudate lobe volume (CV) were measured on MRI. Percentages of individual liver lobe volumes in TLV (including RV/TLV, LMV/TLV, LLV/TLV, and CV/TLV), ratios of SV to individual liver lobe volumes (including SV/RV, SV/LMV, SV/LLV, and SV/CV), and SV/TLV were statistically analyzed to predict EVB. Patients with EVB had lower RV than without EVB (P value = .001), whereas no differences in LMV, LLV, CV, and TLV were found (P values >.05 for all). Among percentages of individual liver lobe volumes in TLV, RV/TLV was lower whereas LMV/TLV and LLV/TLV were greater in patients with EVB than without EVB (P values <.05 for all). SV, ratios of SV to individual liver lobe volumes, and SV/TLV in patients with EVB were larger than without EVB (P values <.05 for all). Among parameters with difference between patients with and without EVB, SV/RV could best predict EVB with an area under receiver operating characteristic curve of 0.84. SV/RLV could best predict EVB in hepatitis B-related cirrhotic patients.

Abbreviations: AUC = area under receiver operating characteristic curve, CV = caudate lobe volume, HVPG = hepatic venous pressure gradient, ICC = interclass correlation coefficient, LLV = left lateral lobe volume, LMV = left medial lobe volume, MELD = model for end-stage liver disease, MR = magnetic resonance, MRI = magnetic resonance imaging, EV = esophagogastroduodenal varices, EVB = esophagogastroduodenal variceal bleeding, ROC = receiver operating characteristic, RV = right lobe volume, SV = spleen volume, TLV = total liver volume, UGE = upper gastrointestinal endoscopy.

Keywords: esophagogastroduodenal variceal bleeding, liver cirrhosis, liver lobe, magnetic resonance imaging, spleen, SV/RV, SV, TLV, RV, LMV, LLV, CV

1. Introduction
Liver cirrhosis is the terminal stage of a variety of chronic liver diseases, especially hepatitis B, which is 1 of the leading causes of chronic liver diseases.[1,2] The major complications of liver cirrhosis include portal hypertension complicated with esophagogastroduodenal varices (EV), ascites, hepatic encephalopathy, hepatorenal syndrome, hypersplenism, and so on.[3] But the most lethal complication is esophagogastroduodenal variceal bleeding (EVb).[4] EV is present in approximately 50% of cirrhotic patients, and EVb occurs in nearly 1 third of cirrhotic patients with EV.[5] Despite the use of standard supportive therapies and new therapeutic methods, the EVb related mortality remains at approximately 15% to 20%.[6]

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Therefore, the prevention of EVB is an extremely significant goal for both the patients with cirrhosis and their physicians, and the effective therapies for preventing EVB exist. Both band ligation and nonselective β-blockers could reduce the relative risk of EVB. To distinguish the cirrhotic patients at high-risk of EVB is the first important step in the prevention of EVB in order to select these cirrhotic patients for prophylactic therapies. The hepatic venous pressure gradient (HVPG) and upper gastrointestinal endoscopy (UGE) are the gold standards for the definitive diagnosis of portal hypertension and EV, respectively. Both of them could assess the risk of EVB. However, they are expensive and invasive procedures, and the cirrhotic patients have poor compliance to them. Therefore, HVPG and UGE are not routinely performed in the patients with advanced cirrhosis. In addition, UGE may cause iatrogenic EVB in the cirrhotic patients with quite serious EV.

The above limitations of HVPG and UGE can be overcome by medical imaging modalities to predict EVB in cirrhotic patients. With the development of medical imaging, multidetector row computed tomography and high-field magnetic resonance imaging (MRI) have been used to perform the studies focusing on the prediction of EV in cirrhotic patients. As reported in these published papers, the liver lobe volumes and spleen volume (SV) have been used to predict the occurrence of EV in the cirrhotic patients but not to predict the occurrence of EVB. To the best of our knowledge, there are no reports on the combinations of liver lobe volume with SV to predict the risk of EVB in the hepatisis B-related cirrhotic patients. Therefore, our study aimed to determine whether the combinations of liver lobe and SVs measured on MRI could predict EVB in hepatitis B-related cirrhotic patients for effective treatment decision making to prevent EVB.

2. Materials and Methods

2.1. Patients

This was a prospective cohort study, which was approved by the ethical committee of the Affiliated Hospital of North Sichuan Medical College. In the study, the informed consent was obtained from each participant and the study would not be detrimental to the treatments of the patients. The study was conducted entirely according to the fundamental principles of the Declaration of Helsinki. In addition, our study was performed according to the descriptions regarding the prospective cohort study by Mann. From February 2017 to January 2019, 119 hospitalized patients with confirmed hepatitis B-related cirrhosis were collected from our hospital based on the following basic inclusion criteria: Hepatitis B-related cirrhosis was diagnosed by the characteristic findings on physical findings, radiological examinations and laboratory tests, according to the clinical practice guidelines established by the American Association for the Study of Liver Diseases involving chronic hepatitis B (2015)]. UGE, biochemical workup and the pretreatment triple-phase enhanced upper abdominal magnetic resonance (MR) scans were performed on the cirrhotic patients within 1 week after initial admission and before the beginning of 2 years’ follow-up; and the patients did not have EVB before the initial hospitalization and during the initial hospitalization. UGE was performed on each cirrhotic patient to confirm the presence of EVB. The biochemical indicators obtained by the previous biochemical workup were used to calculate the model for end-stage liver disease (MELD) score and Child-Pugh classification of the patients. Exclusion criteria included the following: the patients complicated with intrahepatic space-occupying lesions such as liver cancer (n = 7); the patients complicated with portal vein-emboli (n = 2); the patients had the history of surgical procedures involving the liver, such as transjugal intrahepatic portosystemic shunt, hepatic lobectomy, or other related surgery (n = 4); lost to follow-up (n = 3); poor and unsatisfactory quality of the MR images (n = 1); the patients had the history of variceal band ligation or taking nonselective β-blockers (n = 4); or in addition to EVB, the patients had concomitant diseases that could cause gastrointestinal bleeding, such as primary hematologic diseases and ulcerative gastrointestinal bleeding (n = 2). Consequently, 96 cirrhotic participants were enrolled into the study. All patients received conventional liver cirrhosis related treatments during hospitalization. After the patient’s condition was stable, the patients were discharged and the follow-up began.

During the 2 years’ follow-up period after being discharged from hospital, the patients were interviewed by telephone every 2 weeks focusing on EVB-related symptoms, such as hematemesis and melena by the first and second authors, while the patients were encouraged to proactively report the occurrence of EVB-related symptoms. If the patients had EVB-related symptoms, they were asked to go to our hospital to undergo further treatments. UGE was performed to confirm the presence of EVB. The follow-up was stopped if the presence of EVB was confirmed or the follow-up period exceeded 2 years, otherwise follow-up was continued. The cirrhotic patients were divided into the EVB group and non-EVB group according to the outcome of EVB during the follow-up period after being discharged (Fig. 1).

2.2. MR technique

MRI scans were performed with an imported 3.0-T MR scanner (Signa; GE Medical Systems, Milwaukee, WI) in a 32-channel body coil. The patients were placed in a normative supine position when the respiratory signals were established. The routine unenhanced MRI series included the axial unenhanced 3-dimensional liver acquisition with volume acceleration flexible (3D-LAVA-flex) imaging and the axial single-shot fast spin-echo T₂-weighted imaging (SSFSE T₂WI). Before the contrast-enhanced 3D-LAVA-flex scanning, each patient was given an intravenous injection of gadolinium-based contrast agent (Magnesivist; Bayer Schering Berlin, Germany) via a power injector at a 2 ml/s injection rate according to a total dose of 0.2 mmol/kg of body weight, followed by a flush with 20 ml medical normal saline. The parameters of axial unenhanced 3D-LAVA-flex imaging were: repetition time = 4.0 ms, echo time = 2.0 ms, flip angle = 12°, intersection gap = 0 mm, field of view = 36 × 36 cm, slice thickness = 5.2 mm, and matrix = 320 × 224 mm. The parameters for axial SSFSE T₂WI were: repetition time = 2690 ms, echo time = 101 ms, flip angle = 110°, intersection gap = 1 mm, field of view = 34 × 34 cm, slice thickness = 5.2 mm, and matrix = 384 × 384 mm.

![Figure 1](image)

**Figure 1.** The flow chart for collecting participants. EVB = esophagogastric variceal bleeding, UGE = upper gastrointestinal endoscopy.
The parameters for axial contrast-enhanced 3D-LAVA-flex imaging were: repetition time = 4.0 ms, echo time = 2.0 ms, flip angle = 12°, intersection gap = 0 mm, field of view = 36 × 36 cm, slice thickness = 5.2 mm, and matrix = 320 × 224 mm. The scan range was set from the diaphragm to the anatomical lower edge of the liver and spleen, covering the entire liver and spleen.

2.3. Image analysis

The collected MRI data after initial admission were transmitted automatically to a professional workstation (GE Advantage Workstation Version 4.4-09; Sun Microsystems, Palo Alto, CA) for analyses. The enhanced axial 3D-LAVA-flex images included arterial phase images, portal venous phase images and delayed phase images. The analyses of the upper abdominal MRI were finally carried out with the axial portal venous phase images, because we could delineate the border of each liver lobe more accurately on the portal venous phase images than on the arterial phase images or the delayed phase images. As described by the Goldsmith and Woodburne system,[17] the liver of human could be clearly divided into 4 lobes via the hepatic veins and hepatic fissures, including the right lobe, left medial lobe, left lateral lobe and caudate lobe (Fig. 2).

The volumes of the 4 liver lobes and spleen were independently measured by 2 authors (the first author and the corresponding author with 3 and 24 years of experience in cirrhotic patients’ clinical data). In order to accurately obtain the volumes of each liver lobe, the contour of each liver lobe was manually drawn by using the mechanical mouse on portal venous phase images slice by slice, excluding the gallbladder and intrahepatic vessels. The software automatically calculated the area of each slice of liver lobe, the total area of each liver lobe was obtained by summing the areas of each slice of the corresponding liver lobe, and ultimately the volume of each liver lobe was obtained by multiplying the total area of the corresponding liver lobe by the slice thickness. The right lobe volume (RV), left medial lobe volume (LMV), left lateral lobe volume (LLV), and caudate lobe volume (CV) were calculated by the above methods. The total liver volume (TLV) and SV were obtained by the basically similar method as described above. The RV, LMV, LLV, and CV together with TLV and SV from the 2 authors were used to test the interobserver agreement. In order to test the intraobserver agreement, the first author repeated the measurements of the individual liver lobe volumes, TLV and SV 1 week later.

Based on the liver lobe volumes and TLV, the percentages of individual liver lobe volumes in TLV including the ratios of RV to TLV (RV/TLV), LMV to TLV (LMV/TLV), LLV to TLV (LLV/TLV), and CV to TLV (CV/TLV) were calculated. The ratios of SV to individual liver lobe volumes including the ratios of SV to RV (SV/RV), SV to LMV (SV/LMV), SV to LLV (SV/LLV), and SV to CV (SV/CV) together with the ratio of SV to TLV (SV/TLV) were also calculated.

2.4. Statistical analyses

The SPSS (version 25.0, SPSS, Chicago, IL) was used as a tool for the statistical analyses. The statistical test was 2-tailed, and a significant statistical difference was recognized to exist when the P value < .05.

The evaluations of the intra- and interobserver agreements in the RV, LMV, LLV, CV, TLV, and SV were performed with interclass correlation coefficient (ICC) supplemented with 95% confidence interval. The ICC values < 0.20, between 0.21 and 0.40, between 0.41 and 0.60, between 0.61 and 0.80, and > 0.80 were regarded as poor, fair, moderate, good and excellent agreements, respectively.[14]

To predict EVB in hepatitis B-related cirrhotic patients, we compared the clinical characteristics and combinations of liver lobe and SVs before 2 years’ follow-up between EVB and non-EVB groups. The Chi-square test was used to compare the differences in gender and Child-Pugh classification between the EVB group and non-EVB group. To assess the statistical differences in age, Child-Pugh score, MELD score, and the parameters related to liver lobe volumes and SV between the EVB group and non-EVB group, the comparisons were carried out with the Mann–Whitney U test. If there were statistically positive findings in any parameters, the receiver operating characteristic curve (ROC) analyses were used to assess whether the cutoff values of the corresponding parameters could have the ability to predict the occurrence of EVB.
3. Results

3.1. Clinical characteristics

In this cohort, EVB occurred in 31 cases of the 96 participants during the 2 years’ follow-up period, and the rate of EVB was 32.29% (31/96) whereas the remained 65 patients did not have EVB. There were no statistical difference in gender, age, MELD score, Child-Pugh score and Child-Pugh classification between EVB group and non-EVB group as listed in Table 1 (all P values >.05).

3.2. Intra- and interobserver measurement agreement

In all measurements, the intra- and interobserver agreements of RV, LMV, LLV, CV, TLV, and SV are listed in Table 2. Both the intra- and interobserver ICC values of the volume measurements were >0.90 (P values <.001 for all). Therefore, the individual liver lobe volumes, TLV and SV obtained by the first measurement from the first author were finally used for the subsequent analyses.

3.3. Liver lobe volumes and percentages of individual liver lobe volumes: EVB group versus non-EVB group

The comparisons of the parameters including individual liver lobe volumes, TLV, and percentages of individual liver lobe volumes in TLV between the 2 groups are illustrated in Table 3. As for the individual liver lobe volume, the hepatitis B-related cirrhotic patients with EVB had lower RV than without EVB (P value = .001), while no differences in LMV, LLV, CV, and TLV were found between the 2 groups (P values >.05 for all). Regarding percentages of individual liver lobe volumes, RV/TLV was lower, and LMV/TLV and LLV/TLV were greater in the patients with EVB than without EVB (P values <.05 for all) whereas no difference in CV/TLV was found between the 2 groups (P value >.05).

3.4. SV and ratios of it to individual liver lobe volumes: EVB group versus non-EVB group

SV and ratios of SV to individual liver lobe volumes including SV/RV, SV/LMV, SV/LLV, SV/CV, and SV/TLV were compared between the 2 groups (Table 4). All the above-mentioned parameters in the patients with EVB were larger than without EVB (P values <.05 for all).

3.5. ROC analyses of the combinations of liver lobe and SVs to predict EVB

Based on the liver lobe volumes and percentages of individual liver lobe volumes in TLV, SV, and ratios of SV to individual lobe volumes with statistical difference shown by the Mann-Whitney U tests, the ROC analyses were carried out to predict EVB (Table 5 and Fig. 3). We found that SV/RV could best predict EVB with an area under the receiver operating characteristic curve (AUC) of 0.84 among all the above-mentioned quantitative parameters with significant difference between patients with and without EVB.

4. Discussion

The risk of EVB is associated with the severity of cirrhosis and the portal hypertension.[14-19] The morphology of liver and spleen changes with the progress of cirrhosis, and several studies have reported the utility of the liver lobe volume and SV to evaluate the severity of cirrhosis and the degree of portal hypertension.[22-25] For the first time, we explored the feasibility of combinations of liver lobe volume and SV measured on MRI to predict EVB in hepatitis B-related cirrhotic patients for timely treatment decision making to prevent this complication.

Our study showed that there were no statistical differences in MELD score, Child-Pugh score and Child-Pugh classification between the EVB group and non-EVB group. The finding was consistent with the results of the published studies.[15,16] We speculated that the finding might be due to the fact that the MELD score, Child-Pugh score and Child-Pugh classification could only reflect the current severity of cirrhosis, and thus lack the ability to predict the future occurrence of EVB.

Our study found that the hepatitis B-related cirrhotic patients with EVB had lower RV than without EVB while the differences in LMV, LLV, CV, and TLV were not statistically significant between the 2 groups. The decreased hepatic blood perfusion from portal vein could lead to the reduction in the volume of hepatic parenchyma.[26,27] In the cirrhotic patients, liver fibrosis combined with cirrhotic nodules lead to the distortions and stenosis of intrahepatic branches of portal vein and increase the portal vein pressure, and reduce the liver blood flow through portal vein, resulting in the decrease of liver lobe volumes finally.[12] The decrease of the RV may be caused by the fact that the right portal vein enters into the hepatic right lobe directly, and the long intrahepatic length leads to the more serious stenosis and distortion of the right portal vein branch and the significant reduction of blood flow from the right portal vein.[26,28] Because the degree of cirrhosis is more severe in the patients with EVB, the patients with EVB have less blood flow perfusion of right liver lobe, resulting in smaller RV than the patients without EVB. The portal vein branches distributed in the left medial lobe, left lateral lobe and caudate lobe have shorter intrahepatic lengths than the right branch of portal vein in the right
Therefore, the blood perfusion of the left medial lobe, left lateral lobe and caudate lobe could be less affected by cirrhosis, which may lead to no statistical differences in the LMV, LLV, and CV between the patients with and without EVB. Although the RV was smaller in the patients with EVB than without EVB, it did not lead to a significant decrease in TLV in the patients with EVB, and thus TLV was not significantly different between the patients with and without EVB.

As shown in the study, the liver right lobe atrophy was more pronounced in the patients with EVB than without EVB, resulting in a smaller percentage of RV in TLV and relatively higher percentages of LMV and LLV in patients with EVB. CV only accounts for an extremely small portion in TLV, which resulted in the percentage of CV could be not greatly affected by the right lobe atrophy, indicating that no statistical difference existed in the percentage of CV in TLV between patients with and without EVB.

In addition, our study showed that the cirrhotic patients with EVB had greater SV than without EVB. This finding is supported by several published studies. The patients with cirrhosis are at the high-risk of EVB when the patient’s HVPG exceed 12 mm Hg. A published study has shown that there is a significant positive correlation between the SV and

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### Table 3
Comparisons of individual liver lobe volume, total liver volume and percentages of individual liver lobe volume in total liver volume between the 2 groups.

| Parameters                                         | EVB group         | Non-EVB group     | P values |
|----------------------------------------------------|-------------------|-------------------|----------|
| Individual liver lobe volume (cm³)                 |                   |                   |          |
| RV                                                 | 529.05 (391.48, 615.95) | 650.05 (549.48, 788.99) | P = .001 |
| LMV                                                | 115.10 (78.00, 152.23) | 107.43 (85.09, 135.61) | P = .261 |
| LLV                                                | 229.08 (138.61, 332.89) | 206.30 (137.88, 253.50) | P = .160 |
| CV                                                 | 15.87 (12.19, 27.30) | 18.08 (12.62, 24.71) | P = .848 |
| TLV                                                | 927.84 (675.28, 1303.32) | 990.23 (842.58, 1130.76) | P = .102 |
| Percentages of individual liver lobe volume in TLV (%) |                   |                   |          |
| RV/TLV                                             | 58.71 (61.73, 64.08) | 66.95 (59.35, 73.28) | P = .001 |
| LMV/TLV                                            | 14.22 (10.68, 15.43) | 11.20 (9.34, 13.08) | P < .001 |
| LLV/TLV                                            | 26.11 (19.70, 32.24) | 19.93 (14.55, 27.31) | P = .013 |
| CV/TLV                                             | 2.17 (1.55, 2.90) | 1.92 (1.28, 2.42) | P = .288 |

Continuous values are expressed as medians (25% quantile, 75% quantile).

CV = caudate lobe volume, LLV = left lateral lobe volume, LMV = left medial lobe volume, EVB = esophagogastric variceal bleeding, RV = right lobe volume, TLV = total liver volume.

### Table 4
Comparisons of spleen volume, and ratios of spleen volume to individual liver lobe volume and to total liver volume between the 2 groups.

| Parameters                                     | EVB group         | Non-EVB group     | P values |
|------------------------------------------------|-------------------|-------------------|----------|
| Spleen volume (SV, in cm³)                     | 673.06 (420.02, 997.02) | 380.90 (283.90, 459.56) | P = .001 |
| Ratios of SV to individual liver lobe volume   |                   |                   |          |
| SV/RV                                          | 1.28 (0.82, 2.28) | 0.61 (0.40, 0.83) | P < .001 |
| SV/LMV                                         | 6.08 (3.39, 8.71) | 3.75 (2.50, 5.06) | P < .001 |
| SV/LLV                                         | 2.98 (1.72, 5.17) | 1.80 (1.43, 3.02) | P = .006 |
| SV/CV                                          | 35.63 (23.43, 74.96) | 20.28 (14.12, 31.51) | P = .001 |
| Ratio of SV to TLV (SV/TLV)                     | 0.80 (0.42, 1.14) | 0.36 (0.27, 0.56) | P < .001 |

Continuous values are expressed as medians (25% quantile, 75% quantile).

CV = caudate lobe volume, LLV = left lateral lobe volume, LMV = left medial lobe volume, EVB = esophagogastric variceal bleeding, RV = right lobe volume, SV = spleen volume, TLV = total liver volume.

### Table 5
Receiver operating characteristic curve analyses of the statistically different parameters regarding liver lobe volume and/or spleen volume to predict esophagogastric variceal bleeding.

| Parameters                                         | Cutoff | AUC  | Sensitivity (%) | Specificity (%) |
|----------------------------------------------------|--------|------|-----------------|-----------------|
| Individual liver lobe volume (RV, in cm³)          | 616.28 | 0.71 | 77.4            | 61.5            |
| Percentages of individual liver lobe volume in TLV (%) |        |      |                 |                 |
| RV/TLV                                             | 66.7   | 0.72 | 87.1            | 52.3            |
| LMV/TLV                                            | 13.69  | 0.73 | 61.3            | 87.7            |
| LLV/TLV                                            | 17.87  | 0.66 | 90.3            | 41.5            |
| Spleen volume (SV, in cm³)                         | 657.92 | 0.78 | 64.5            | 90.8            |
| Ratios of SV to individual liver lobe volume       |        |      |                 |                 |
| SV/RV                                             | 0.85   | 0.84 | 74.2            | 78.5            |
| SV/LMV                                            | 5.74   | 0.73 | 54.8            | 87.7            |
| SV/LLV                                            | 2.43   | 0.67 | 74.2            | 67.7            |
| SV/CV                                             | 31.33  | 0.72 | 61.3            | 75.4            |
| Ratio of SV to TLV (SV/TLV)                        | 0.79   | 0.81 | 58.1            | 93.8            |

AUC = area under the receiver operating characteristic curve, CV = caudate lobe volume, LLV = left lateral lobe volume, LMV = left medial lobe volume, RV = right lobe volume, SV = spleen volume, TLV = total liver volume.
resulting in the enlargement of spleen. In addition, we found the enlargement of splenic parenchyma, and finally, hypertension. Portal hypertension leads to splenic congestion and the hyperplasia of the splenic parenchyma. The result may be based on the fact that the patients with EVB had smaller RV and greater SV, resulting in more significant differences in SV/RV between patients with and without EVB compared with other parameters. Therefore, we can recommend that SV/RV could be considered as the best parameter to predict the presence of EVB.

In conclusion, our study showed that the intra- and interobserver agreements of individual liver lobe volumes, TLV and SV were excellent, suggesting that the repeatability of volume measurement was reliable, and the volume measurement error would not be a limiting factor for this study. There are some limitations in this study. Firstly, the sample size of our study is relatively small, especially the number of the cirrhotic patients with EVB is small. Therefore, the future work is to collect multi-center and large-sample data to confirm our findings. Secondly, MRI may not be the preferred imaging examination for the patients with cirrhosis. However, as a safe and radiation-free imaging modality, MRI has received increasing attention in the assessment of liver diseases.

In conclusion, our study showed that the right liver lobe atrophy and splenomegaly could be more significant in the hepatitis B-related cirrhotic patients with EVB than without EVB. We found that the SV/RV could be considered as the best parameter to predict EVB in the cirrhotic patients when compared with any other volume parameters of liver and spleen. We hope that our finding will be helpful to select cirrhotic patients with high-risk EVB to prevent occurrence of this fatal complication.

**Author contributions**

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