# TITLE:

VALIDATION OF THE VIBe INTRAOPERATIVE BLEEDING SCALE IN LIVER SURGERY.
PROSPECTIVE AND MULTICENTER STUDY

## PROMOTER:

Institute for Health Research Aragón

## RESEARCH TEAM:

## Principal investigators:

**Mario Serradilla Martin**
Institute for Health Research Aragón
Division of Hepato-Pancreato-Biliary Surgery
Department of Surgery
Miguel Servet University Hospital
Paseo Isabel La Católica, 1-3
50009 Zaragoza (Spain)

**Daniel Aparicio López**
Department of Surgery
Miguel Servet University Hospital
Paseo Isabel La Católica, 1-3
50009 Zaragoza (Spain)

**Jose Manuel Ramia Angel**
Head, Department of Surgery
Alicante General University Hospital
Painter Baeza, 11
03010 Alicante (Spain)

## Research collaborators:

Attached in ANNEX I.

## Correspondence:

Mario Serradilla Martin
Division of Hepato-Pancreato-Biliary Surgery
Department of Surgery
Miguel Servet University Hospital
Paseo Isabel La Católica, 1-3
50009 Zaragoza (Spain)
email: marioserradilla@hotmail.com / mserradilla@salud.aragon.es

**Study design:** Mario Serradilla Martín, José Manuel Ramia Ángel.
**Study protocol:** Daniel Aparicio López, Mario Serradilla Martín, José Manuel Ramia Ángel.
**Data collection notebook:** Daniel Aparicio López, Mario Serradilla Martín, José Manuel Ramia Ángel.

Prospective multicenter study, supported by the Hepato-Pancreato-Biliary Surgery Division of the Spanish Association of Surgeons (AEC) and the Spanish Chapter of the International Association of Hepato-Pancreato-Biliary Surgery (IHPBA).

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| **AEC** | Spanish Association of Surgeons |
| **CCI** | Comprehensive Complication Index |
| **CEICA** | Research Ethics Committee of Aragon |
| **FDA** | Food and Drug Administration |
| **GCP** | Good Clinical Practices |
| **IHPBA** | International Association of Hepato-Pancreato-Biliary Surgery |
| **ISGLS** | International Study Group of Liver Surgery |
| **JCR** | Journal Citation Reports |
| **VIBe** | Validated Intraoperative Bleeding Scale |

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**ABSTRACT**

**Introduction.** Surgical hemostasis has become one of the fundamental principles for the advancement of surgery. The use of hemostatic agents is standard in many surgical specialties, although the lack of consensus or standardized classifications to determine intraoperative bleeding has led to their inappropriate selection on many occasions. The recommendations of international organizations highlight the need for a bleeding severity scale validated in clinical studies that allows selecting the hemostatic agent that best suits each case.

**Objective.** The primary objective is to validate the VIBe scale (Validated Intraoperative Bleeding Scale) in liver surgery. The secondary objectives are: to assess the repeatability, reproducibility and usefulness of the scale in this type of surgery, and determine the relationship between type of bleeding and hemostatic used.

**Methods.** Prospective multicenter observational study including all liver resections performed in participating hospitals in the study period. The participating collaborating researchers will be responsible for collecting the data, as well as for communicating them to the study coordinators.

**Strengths.** Medium / high volume Liver Surgery Units of Spain participate in this multicenter study, thus being able to recruit a large sample size, which will allow us to collect highly detailed, representative and reliable information on the results obtained.

**Need for the study.** Despite the large number of liver resections performed annually, intraoperative hemostasis is performed using different topical hemostats. However, there is no validated scale that allows stratifying bleeding and selecting the hemostatic agent that best suits each clinical situation.

**Limitations.** The study is multicenter in nature, so there may be selection or information biases when dealing with centers with different criteria and surgical indications. The quality of the outcome measurement is limited by the possible heterogeneity between centers and the quantification of intraoperative bleeding.

## 1. BACKGROUND

Surgical hemostasis has become one of the fundamental principles for the advancement of surgery[1]. The use of hemostatic agents is standard in many surgical specialties[2-6], with greater use in major surgeries[7-8]. Inadequate hemostasis significantly increases the risk of perioperative morbidity and mortality[9-10], healthcare costs and the use of resources[11-14]. The need for hemostasis has led to the development of various topical hemostatic agents[15-17].

Clinical studies that have analyzed the use of topical hemostats have not used standardized definitions or classifications to determine the severity of intraoperative bleeding[18-19], partly due to a lack of consensus on the definition of the severity of bleeding and partly due to the severity of bleeding. lack of requirements to do so. This has led many surgeons to an inadequate selection of hemostats for different bleeding situations, the results being inefficient[8]. Using standardized criteria, the results of clinical studies can be compared to determine the effectiveness of hemostatic agents.

The FDA (Food and Drug Administration) requires the use of a bleeding severity scale validated in clinical studies investigating hemostatic agents. The VIBe (Validated Intraoperative Bleeding Scale) for intraoperative bleeding was developed in 2017[20]. This scale has been validated by a large number of expert surgeons from all specialties, but in an animal model. However, it has not yet been clinically validated.

Liver surgery is one of the surgeries where intraoperative bleeding is more important. In Spain, around 5000 liver resections are performed annually, not including liver transplants. It is, therefore, a perfect framework to validate the applicability of the VIBe scale of severity of intraoperative bleeding.

In order to evaluate the viability of a prospective clinical study in liver surgery, a parallel project has been worked on based on the evaluation of the applicability of the VIBe scale, carried out by liver surgeons by reviewing the original video recordings described in the VIBe scale[28]. Forty-seven surgeons were selected from 10 medium/high-volume liver surgery centers, all of them reference centers (same centers that will participate in the prospective study). 5 of the 10 hospitals perform liver transplants. These centers have a mean reference population of 922,506 ± 225,603 patients. The mean number of major hepatectomies per year is 23 ± 16, the number of minor hepatectomies 56 ± 24, and the number of liver transplants 40 ± 27. 40.5% of all hepatectomies are performed by a minimally invasive approach.

The 47 surgeons viewed 14 videos used by *Lewis et al.*[20] for the validation of the original VIBe scale. 63.3% of the participating surgeons were men with a mean age of 41.6 years. 17% were unit / department heads and 83% were senior surgeons. The mean experience was 9.3 years, and the majority were experts (21.3%) or with advanced knowledge (53.2%) in minimally invasive surgery. Only 23.4% had prior knowledge of the VIBe scale, but all surgeons used hemostats in their daily clinical practice. The VIBe scale achieved a mean intraobserver agreement of 0.985 and an interobserver agreement of 0.929, neither of which was influenced by the experience of the surgeon or the volume of surgeries per year. The average rating for all videos was 67% correct, in line with the original validation. Most surgeons considered that the scale represented the range of severity of bleeding in their procedures (91%), relevant to assess intraoperative hemostasis in clinical studies (96%) and clinical practice (87.2%), useful in CMI (96%), and also to differentiate hemostatic agents (81%).

The data of the analysis are shown in Table 1.

| | Kendall's coefficient of agreement | Degree of concordance |
|---|---|---|
| **Intra-observer agreement** | | |
| All surgeons (N=47) | 0.985 | Excellent |
| Depending on the surgeon's experience | | |
| High experience (N=23) | 0.990 | Excellent |
| Low experience (N=24) | 0,981 | Excellent |
| Depending on the number of surgeries/ year | | |
| High number (N=20) | 0.995 | Excellent |
| Low number (N=27) | 0.979 | Excellent |
| **Interobserver agreement** | | |
| All surgeons (N=47) | 0.929 | Excellent |
| Depending on the surgeon's experience | | |
| High experience (N=23) | 0.941 | Excellent |
| Low experience (N=24) | 0.922 | Excellent |
| Depending on the number of surgeries / year | | |
| High number (N=20) | 0.940 | Excellent |
| Low number (N=27) | 0.923 | Excellent |
| A Kendall coefficient of 0.70 or more was considered evidence of a scoring system with appreciable agreement, a coefficient of 0.80 or more was considered good agreement, and a coefficient of 0.90 or more excellent agreement. . The median experience was 7 years: low experience was considered ≤ 7 years; It was considered high experience> 7 years. The median number of surgeries per year was 35: a low number of surgeries ≤ 35 surgeries per year was considered; The number of surgeries> 35 surgeries per year was considered high. | | |

**Table 1.** Correct score compared to the publication of *Lewis et al*. 2017 and interobserved agreement.

With these preliminary data, based on the video classification exercise, we can conclude that the VIBe scale is useful for the assessment of the severity of bleeding performed by liver surgeons. Therefore, an assessment of the severity of intraoperative bleeding using the scale in actual liver surgery is feasible. Our goal is to publish these results independently before starting the clinical observation record.

To evaluate the clinical applicability, a prospective registry of patients undergoing liver surgery has been designed in the 10 selected Spanish centers.

Demographic and preoperative, intraoperative and postoperative data will be collected (ANNEX II). Intraoperative bleeding will be measured according to the VIBe scale at two points of the surgical intervention: the maximum bleeding and at the end of the surgery. Data will be collected on the type of hemostatic or surgical strategy that has been carried out to correct bleeding (i.e. pressure, suture, coagulation, hemostatic, etc.) and other data related to bleeding (blood loss, units of blood transfused, etc.). Postoperative complications will be classified according to the Clavien-Dindo classification and the CCI (Comprehensive Complication Index) (ANNEX III). Major complications are defined as those with a Clavien-Dindo ≥ IIIa. The classification of liver failure and postoperative bleeding are defined following the International Study Group of Liver Liver Surgery (ISGLS) classifications (ANNEX III). An online database will be generated (CASTOR®, CIWIT BV, Amsterdam) and at the end of the registration a statistical analysis of the data will be performed to determine the applicability and usefulness of the VIBe scale in liver surgery, as well as to determine the relationship between the type of bleeding, the hemostatic measurements used, the success rate of the hemostatic measurements, and the bleeding-related complications.

Despite the extensive literature published on liver surgery, there is no scientific evidence that allows us to have validated scalds that quantify the severity of intraoperative bleeding and, consequently, select which is the best hemostatic procedure that is adapted to each case. All of this has repercussions on patient safety, increased postoperative morbidity and mortality, as well as the inappropriate use of healthcare resources and consequently increased costs.

This prospective multicenter study in national centers that perform Liver Surgery aims to evaluate and validate a scale that allows quantifying intraoperative bleeding in liver surgery.

## 2. HYPOTHESIS

The VIBe scale for the severity of intraoperative bleeding has only been validated in an animal model since its inception. Liver surgery is a type of surgery where intraoperative bleeding occurs frequently and can have a major impact on the results. It is, therefore, a perfect framework to apply the VIBe scale for intraoperative bleeding in humans.

## 3. OBJETIVES

- **Primary objective:** to validate the VIBe scale for intraoperative bleeding in liver surgery.

- **Secondary objectives:**
  - Assess the repeatability, reproducibility and usefulness of the scale in this type of surgery.
  - Determine the relationship between type of bleeding and hemostatic used, the success rate of hemostatic measurements, and complications related to bleeding.

## 4. METHODS

It is a prospective multicenter registry lasting 12 months (this period can be lengthened if the stipulated number of patients has not been reached) in which 10 units of reference of HPB Surgery participate in Spain with medium/high volume of liver surgery . This registry includes all the elderly patients operated on in the participating Spanish centers who underwent liver surgery in the period described. The registry will remain open until the sample size is recruited for a further 4 months to include postoperative morbidity and mortality at 90 days.

The key point of the study is to determine the degree of intraoperative bleeding evaluated with the VIBe scale. Because bleeding episodes can be numerous during a hepatectomy, it is considered impossible to measure each bleeding individually. According to the collaborating researchers, it has been considered appropriate to assess it at two selected moments: the moment of greatest bleeding and at the end of the surgery. An intraoperative record sheet (ANNEX IV) will be prepared and completed according to the statements of the main or assistant surgeon and will be reviewed and finally signed by the main surgeon at the end of the procedure. In the same way, blood losses (amount of fluid in the suction container minus serum used for flushing), the units of blood transfused and the lowest hemoglobin value during admission (compared to baseline hemoglobin) will be quantified. ). The rest of the data will be collected at the time of discharge and 3 months after surgery.

### 4.1. Patient and design

- **Inclusion criteria:** patients scheduled for liver surgery, by open or minimally invasive approach, regardless of diagnosis; ASA score <4; age ≥ 18; who have signed the informed consent.

- **Exclusion criteria:** patients with contraindications for liver surgery; emergency surgical interventions; patients <18 years; patients who have not signed the informed consent.

### 4. 2. Participating centers

Ten national centers of moderate-high volume in liver surgery participated in this study, all of them reference centers, which participated in the first phase of the study with the visualization of the videos. The dissemination and knowledge of the study will be carried out through the HPB Surgery Section of the

Spanish Association of Surgeons (AEC), as well as the Spanish Chapter of the International Association of Hepato-Pancreato-Biliary Surgery (IHPBA). When confirming their participation, the participating centers will designate a contact person.

### 4. 3. Follow-up time

Classically, morbidity and mortality data are recorded in the immediate postoperative period (30 days). However, liver surgery is a type of surgery in which complications can occur beyond 30 days, so the international scientific community has agreed to record complications after 90 days.

### 4.4. Definitions

Patient comorbidities will be classified using the Charlson Comorbidity Index[29]. Postoperative complications will be classified using the Clavien-Dindo[30] Classification of Surgical Complications and the Comprehensive Complication Index (CCI)[31]. Major complications are those defined as Clavien-Dindo grade IIIa or higher. To collect complications, the medical and nursing notes of each electronic or physical record of each patient included in the project will be contrasted. For the specific complications of liver surgery, the definitions of the International Study Group of Liver Liver Surgery (ISGLS) of liver failure[32] and postoperative bleeding[33] will be used. Complications, readmissions and mortality will be measured at 90 postoperative days, through the medical history and, if necessary, by telephone communication with the patient or relatives (ANNEX III).

### 4.5. Data record

Each participating center will designate a contact person, responsible for data collection, and all communication with the study coordinators. Subsequently, each contact person will receive a login code and passwords for the online electronic case report form (CRDe) environment (CASTOR®, CIWIT B.V., Amsterdam). Each data collector will receive a separate login account from which the lead study coordinators can monitor all activity. All data collection will be carried out in accordance with the Good Clinical Practice (GCP) guidelines.

The variables collected in said form are shown in ANNEX II.

### 4.6. Sample size

Based on an estimated population size of 5000 liver surgeries per year in Spain, a sample size of 259 cases will be selected to achieve a margin of error of 5% with a confidence level of 90%.

Based on the normal distribution, the sample size n and the margin of error E are given by:

$x = Z\ (c / 100)\ 2r\ (100-r)$
$n = N\ x / ((N-1)\ E2 + x)$
$E = Sqrt\ [(N - n)\ x / n\ (N-1)]$

Where N is the size of the population, r is the fraction of responses (set at 50% as the most conservative assumption) and Z (c / 100) is the critical value for the confidence level c[21].

### 4.7. Statistical analysis

Depending on the number of cases contributed by each collaborating hospital, a retrospective analysis will be carried out to detect the power of the differences observed in the data. The variables of interest will be described in univariate and bivariate tables according to the study groups. For comparisons between groups, parametric (t-student, ANOVA) and non-parametric (Mann-Whitney, Kruskal-Wallis) tests will be used in continuous variables depending on their distribution and Fisher or chi-square tests for categorical variables.

To investigate the relationship between different variables, correlation analysis and / or linear regression and bi or multivariate logistic will be used. In addition, the longitudinal variation of certain variables of interest will be studied, for this, Kaplan-Meier estimators and bi or multivariate analysis using Cox models will be carried out. The analyzes will be carried out with the statistical software R. Statistical significance will be considered for values of $p < 0.05$.

## 5. ETHICAL ASPECTS

- **Risk / benefit balance.** This is a prospective registry of patients undergoing liver surgery. It is a common procedure that does not require the performance of any extraordinary measure.
- An insurance policy is not necessary to not carry out any invasive treatment.
- **Treatment of personal data.** In accordance with the Organic Law on Personal Data Protection of December 6, 2018, in accordance with the General Data Protection Regulation, patients participating in the study will be adequately informed about the data to be collected and for what purpose. They will use the data, as well as the right of access, modification, opposition, cancellation, portability and limitation at all times. Those responsible for data treatment will have the necessary technical and organizational measures, in the terms derived from the regulations (articles 9.2.j), 89.1 and 32 RGPD), complying

with the requirements established in sections 2.d) , f) and g) of DA 17 of LO 3/2018.

At no time will identifying data of the patient be included in the study base and no one except the research team of each hospital will be able to access the identity of the patient. The data will be included in the environment of the electronic online case report form (CASTOR®, CIWIT B.V., Amsterdam), which complies with current European and American data protection regulations. All editing and audit trails will be logged in accordance with Good Clinical Practice (GCP) guidelines.

- At no time does the study interfere with the care tasks of the center, does not increase the waiting lists or imply a distribution of resources that may affect the principle of justice. In no case will the usual practice be altered.
- Each patient will be given the informed consent that they must sign to be included in the registry (ANNEX V).
- This study has a purely observational design, so it will not carry out any type of intervention on the recruited individuals. The study will be carried out in accordance with the Declaration of Helsinki (last modification, Brazil, 2013) and current Spanish legislation (Ministerial Order SAS / 3470/2009, regarding the performance of observational studies and Law 14/2007, on biomedical research) .
- This study will have the approval of the Research Ethics Committee of Aragon (CEICA).

## 6. AUTHORSHINP AND PUBLICATION POLICY

Authorship will be based on the guide of the International "Committee of medical Journal Editors" [34]. The study coordinators will occupy the first and last positions of authorship (DAL, MSM and JMRA). All centers will have the right to include 3 authors in the publications generated by the study. The order will be determined by the number of cases contributed and if there is a tie of cases in

alphabetical order. The data obtained will be communicated to the CEIC Law14/2007 and published.

The data generated by the study will be sent to journals with a contrasted impact factor indexed in the Journal Citation Reports (JCR). In the same way, they will be sent as communications to international conferences of reference of HPB Surgery (IHPBA/E-AHPBA congress/ESSO Congress).

## 7. TIMELINE

| 2021/2023 | Oct | Nov | Dec | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec | Jan | Feb | Mar | Apr |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Protocol | | | | | | | | | | | | | | | | | | | |
| Ethics Committee | | | | | | | | | | | | | | | | | | | |
| Identification of centers | | | | | | | | | | | | | | | | | | | |
| Data Collect | | | | | | | | | | | | | | | | | | | |
| Analysis of data | | | | | | | | | | | | | | | | | | | |
| Manuscript | | | | | | | | | | | | | | | | | | | |

## 8. FUNDING

This study has received the Investigator Initiated Research (IIR) grant from Baxter S.L.
https://www.baxter.com/our-story/fueling-collaborative-innovation/research-continuing-education-grants

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## 10. ANEXXES

## ANNEX I. PARTICIPATING HOSPITALS AND MAIN RESEARCHERS OF EACH CENTER.

| HOSPITAL | CITY | PRINCIPAL RESEARCH | POSITION |
|---|---|---|---|
| Miguel Servet | Zaragoza | Mario Serradilla Martín | Senior HPB surgeon |
| General Universitario | Alicante | José Manuel Ramia Ángel | Head of Service |
| Virgen del Rocío | Sevilla | Miguel Ángel Gómez Bravo | Head of HPB department |
| La Princesa | Madrid | Elena Martín Pérez | Head of Service |
| Mutua de Tarrasa | Tarrasa | Esteban Cugat Andorrá | Head of HPB department |
| Germán Trias y Pujol | Badalona | Esteban Cugat Andorrá | Head of HPB department |
| Josep Trueta | Girona | Santiago López Ben | Head of HPB department |
| Complejo Universitario | Badajoz | Gerardo Blanco Fernández | Head of Service |
| Clínico Universitario | Valencia | Luis Sabater Ortí | Head of HPB department |
| Gregorio Marañón | Madrid | José Manuel Asencio Pascual | Senior HPB surgeon |

**ANNEX II. DATA COLLECTION NOTEBOOK.**

- Hospital.
- Patient identification number.
- Date of birth.
- Sex:
    - Male.
    - Female.
- Weight (kg).
- Height (m).
- BMI (Kg / m2)
- ASA:
    - I.
    - II.
    - III.
    - IV.
- Charlson comorbidity index:
    - DM without target organ involvement.
    - Diabetes with target organ involvement.
    - Myocardial infarction.
    - Coronary heart disease.
    - Peripheral vascular disease.
    - Cerebrovascular disease.
    - Arterial hypertension.

  - Alcoholism.
  - Thromboembolic disease.
  - Arrhythmia.
  - Dementia.
  - COPD.
  - Connective tissue disease.
  - Peptic ulcer.
  - Mild liver disease (without portal hypertension, includes chronic hepatitis).
  - Hemiplegia.
  - Moderate-severe kidney disease.
  - Leukemia (acute or chronic).
  - Lymphoma.
  - Moderate or severe liver disease.
  - Solid tumor with metastasis.
  - AIDS (not just HIV positive).
- Surgical history:
  - Cholecystectomy.
  - Hepatectomy.
  - Other supramesocolic surgery.
  - Inframesocolic surgery.
  - Others.
  - No
- Underlying disease:
  - Liver metastasis from colorectal carcinoma
  - Liver metastasis from neuroendocrine tumor
  - Liver metastasis from no coloretal carcinoma or neuroendocrine tumor
  - Hepatocarcinoma.
  - Cholangiocarcinoma
  - Adenoma.

  - Focal nodular hiperplasia.
  - Others.
- Affected liver segments (intraoperatively)
  - I.
  - II.
  - III.
  - IVa.
  - IVb.
  - V.
  - VI.
  - VII.
  - VIII.
- Neoadjuvant chemotherapy
  - Yes.
  - No.
- Time elapsed from diagnosis to start of treatment (days).
- Date of surgery
- Previous portal embolization:
  - Yes.
  - No.
- Previous volumetry:
  - Yes
  - No.
- Functional residual volume (cc)
- Two-stage surgery::
  - Yes.
  - No.
- Reverse surgery:
  - Yes.
  - No.
- Surgical approach:

  - Open (laparotomy)
  - Laparoscopy
  - Robotic
  - Conversion
- Type of liver (macroscopic):
  - Normal.
  - Steatosis
  - Fibrosis
  - Chemotherapy-induced liver injury Cirrhosis
- Type of surgery:
  - Left lateral sectionlectomy (2 and 3)
  - Bisegmentectomy (5 and 6)
  - Right anterior sectionlectomy (5 and 8)
  - Right posterior sectionlectomy (6 and 7)
  - Left hepatectomy (2, 3 and 4)
  - Right hematopathy (5, 6, 7 and 8)
  - Central hepatectomy (4, 5 and 8)
  - Extended right hepatectomy (4, 5, 6, 7 and 8)
  - Extended left hepatectomy (2, 3, 4, 5 and 8)
  - Atypical resection 1
  - Atypical resection 2
  - Atypical resection 3
  - Atypical resection 4a
  - Atypical resection 4b
  - Atypical resection 5
  - Atypical resection 6
  - Atypical resection 7
  - Atypical resection 8
  - Anatomical resection segment 1
  - Anatomical resection segment 2
  - Anatomical resection segment 3

  - Anatomical resection segment 4a
  - Anatomical resection segment 4b
  - Anatomical resection segment 5
  - Anatomical resection segment 6
  - Anatomical resection segment 7
  - Anatomical resection segment 8
- Other associated procedures:
  - Radiofrequency
  - Microwave.
  - Atypical resection
  - Others
- Operative time (min).
- Bleeding (ml).
- Units of blood transfused:
- Type of bleeding (major intraoperative bleeding):
  - 0: no bleeding (<1 mL / min).
  - 1: mild (1-5 mL / min)
  - 2: moderate (5-10 mL / min).
  - 3: severe (10-50 mL / min).
  - 4: very severe (> 50 mL / min).
- Type of hemostasis performed:
  - Compression
  - Coagulation
  - Suture
  - Application of hemostatic agent
  - Name of hemostatic
- Clamping time (min).
- Complications:
  - Yes.
  - No.
- Complications (Clavien-Dindo):

  - I
  - II
  - IIIa
  - IIIb
  - IVa
  - IVb
  - V
- Comprenhensive Complication Index.
- Hemorrhage
  - No.
  - A.
  - B.
  - C.
- Liver failure
  - No.
  - Mild.
  - Moderate.
  - Severe.
- Biliary fistula:
  - Yes.
  - No.
- Bilioma:
  - Yes.
  - No.
- Intra-abdominal collection:
  - Yes.
  - No.
- Reintervention:
  - Yes.
  - No.
- Type:

  - Percutaneous drainage.
  - ERCP.
  - Surgical reintervention.
  - Interventional X-ray
- Medical complication:
  - Septic shock.
  - IAM.
  - Cardiac arrest.
  - DVT or pulmonar embolism.
  - ACV/AIT.
  - Others.
- ICU stay (días).
- Total stay (days):
- Postoperative transfusión:
  - Yes.
  - No.
- Units of blood:
- Reentry:
  - Yes.
  - No.
- Cause:
- Hemoglobine:
  - Preoperative.
  - Lower during the hospital stay.
- Need for IV or PO iron:
  - Yes.
  - No.
- **Follow-up at 3 months:**
- Free from disease:
  - Yes.
  - No.

- Recurrence date:
- Death:
    - Yes.
    - No.
- Date of death or last visit.

## ANNEX III. CLASSIFICATIONS USED

### CLAVIEN-DINDO CLASSIFICATION OF SURGICAL COMPLICATIONS.

*Dindo D, Demartines N, Clavien P-A. Classification of surgical complications. Ann Surg. 2004;240:205–213.*

| Degree | Definition |
|---|---|
| I | Any deviation from the normal postoperative course without need of intervention beyond the administration of anti-emetics, antipyretics, analgesics, diuretics, electrolytes, and psychical therapy[a] |
| II | Complication requiring pharmacological treatment with other medicines beyond the ones used for complications of degree I |
| III | Complications requiring surgical, endoscopic, or radiological intervention |
| III-a | Intervention without general anesthesia |
| III-b | Intervention under general anesthesia |
| IV | Life-threatening complication requiring admission to intensive care unit |
| IV-a | Uniorgan dysfunction (including dialysis) |
| IV-b | Multiorgan dysfunction |
| V | Death |

[a] This degree also includes wound infections opened at the bedside.

Suffix "d"

If the patient suffers a complication at the time of discharge, the suffix “d” (for disability) is added to the degree of the complication (resection of the pancreatic remnant is included). This suffix indicates the need for follow-up to fully evaluate the complication.

* Regarding RVG: The placement of a central line for TPN or nasojejunal tube by endoscopy in a grade IIIa complication. However, if the central line or nasojejunal tube has been placed during surgery, then TPN or enteral nutrition is a grade II complication.

† Cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, excluding transient ischemic attacks.

## COMPREHENSIVE COMPLICATION INDEX

*Slankamenac K, Nederlof N, Pessaux P, et al. The comprehensive complica- tion index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. Ann Surg. 2014;260:753 – 757.*

Website: https://www.assessurgery.com/

## CLASSIFICATION OF POSTOPERATIVE BLEEDING

*Rahbari N, Garden J, Padbury R, Maddern G, Koch M, Hugh T, et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). HPB. 2011; 13(8): 528-35.*

| | | |
|---|---|---|
| *Definition* | Post-hepatectomy haemorrhage (PHH) is defined as a drop of haemoglobin level >3 g/dl after the end of surgery compared to postoperative baseline level and/or any postoperative transfusion of PRBCs for a falling hemoglobin and/or the need for invasive re-intervention (e.g. embolization or re-laparotomy) to stop bleeding.<br>To diagnose PHH (and to exclude other sources of haemorrhage) evidence of intraabdominal bleeding should be obtained such as frank blood loss via the abdominal drains if present (e.g. haemoglobin level in drain fluid >3 g/dl) or detection of an intra-abdominal haematoma or active haemorrhage by abdominal imaging (ultrasound, CT, angiography). Patients who are transfused immediately postoperatively for intra-operative blood loss by a maximum of two units of PRBCs (i.e. who do not have evidence of active haemorrhage) are *not* diagnosed with PHH. | |
| *Grading* | A | PHH requiring transfusion of up to 2 units of PRBCs |
| | B | PHH requiring transfusion of >2 units of PRBCs but manageable without invasive intervention |
| | C | PHH requiring radiological interventional treatment (e.g. embolization) or re-laparotomy |

## POSTOPERATIVE BILIARY FISTULA CLASSIFICATION

*Brooke M, Figueras J, Ullah S, Rees M, Vauthey JN, Hugh TJ, et al. Prospective evaluation of the International Study Group for Liver Surgery definition of bile leak after a liver resection and the role of routine operative drainage: an international multicentre study. HPB. 2015. 17(1):46-51.*

| Grade | Description |
|---|---|
| A | Bile leakage requiring no or little change in patient's clinical management |
| B | Bile leakage requiring a change in patient's clinical management (e.g. additional diagnostic or interventional procedures) but manageable without relaparotomy, or a grade A bile leakage lasting for >1 week |
| C | Bile leakage requiring relaparotomy |

**POSTOPERATIVE LIVER FAILURE CLASSIFICATION**

*Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, Makuuchi M, Dematteo RP, Christophi C, Banting S, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Yokoyama Y, Fan ST, Nimura Y, Figueras J, Capussotti L, Büchler MW, Weitz J. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149(5):713-24.*

| | *Criteria for PHLF Grade A* | *Criteria for PHLF Grade B* | *Criteria for PHLF Grade C* |
|---|---|---|---|
| Specific treatment | Not required | Fresh-frozen plasma<br>Albumin<br>Daily diuretics<br>Noninvasive ventilation<br>Transfer to intermediate/ intensive care unit | Transfer to the intensive care unit<br>Circulatory support (vasoactive drugs)<br>Need for glucose infusion<br>Hemodialysis<br>Intubation and mechanical ventilation<br>Extracorporeal liver support<br>Rescue hepatectomy/liver transplantation |
| Hepatic function | Adequate coagulation (INR <1.5)<br>No neurological symptoms | Inadequate coagulation (INR ≥1.5 <2.0)<br>Beginning of neurologic symptoms (ie, somnolence and confusion) | Inadequate coagulation (INR ≥2.0)<br>Severe neurologic symptoms/ hepatic encephalopathy |
| Renal function | Adequate urine output (>0.5 mL/kg/h)<br>BUN <150 mg/dL<br>No symptoms of uremia | Inadequate urine output (≤0.5 ml/kg/h)<br>BUN <150 mg/dL<br>No symptoms of uremia | Renal dysfunction not manageable with diuretics<br>BUN ≥150 mg/dL<br>Symptoms of uremia |
| Pulmonary function | Arterial oxygen saturation >90%<br>May have oxygen supply via nasal cannula or oxygen mask | Arterial oxygen saturation <90% despite oxygen supply via nasal cannula or oxygen mask | Severe refractory hypoxemia (arterial oxygen saturation ≤85% with high fraction of inspired oxygen) |
| Additional evaluation | Not required | Abdominal ultrasonography/CT<br>Chest radiography<br>Sputum, blood, urine cultures<br>Brain CT | Abdominal ultrasonography/CT<br>Chest radiography/CT<br>Sputum, blood, urine cultures<br>Brain CT<br>ICP monitoring device |

# ANNEX IV. INTRAOPERATIVE REGISTRATION DOCUMENT.

| | | | |
|---|---|---|---|
| **SURGICAL APPROACH** | Open (laparotomy) | | |
| | Laparoscopy | | |
| | Robotic | | |
| | Conversion | | |
| **TYPE OF LIVER (macrosopic)** | Normal | | |
| | Steatosis | | |
| | Fibrosis | | |
| | Chemotherapy-induced liver injury | | |
| | Cirrhosis | | |
| **TYPE OF SURGERY** | Left lateral sectionlectomy (2 and 3) | | |
| | Bisegmentectomy (5 and 6) | | |
| | Rigth anterior sectionlectomy (5 and 8) | | |
| | Right posterior sectionlectomy (6 and 7) | | |
| | Left hepatectomy (2, 3 and 4) | | |
| | Right hepatectomy (5, 6, 7 y 8) | | |
| | Central hepatectomy (4, 5 and 8) | | |
| | Extended right hepatectomy (4, 5, 6, 7 and 8) | | |
| | Extended left hepatectomy (2, 3, 4, 5 and 8) | | |
| | Atypical resection 1 | | |
| | Atypical resection 2 | | |
| | Atypical resection 3 | | |
| | Atypical resection 4a | | |
| | Atypical resection 4b | | |
| | Atypical resection 5 | | |
| | Atypical resection 6 | | |
| | Atypical resection 7 | | |
| | Atypical resection 8 | | |
| | Anatomical resection segment 1 | | |
| | Anatomical resection segment 2 | | |
| | Anatomical resection segment 3 | | |
| | Anatomical resection segment 4a | | |
| | Anatomical resection segment 4b | | |
| | Anatomical resection segment 5 | | |
| | Anatomical resection segment 6 | | |
| | Anatomical resection segment 7 | | |
| | Anatomical resection segment 8 | | |
| **OTHERS ASSOCIATED PROCEDURES** | Radiofrequency | | |
| | Microwave | | |
| | Atypical resectión | | |
| | Others | | |
| **OPERATIVE TIME (min)** | | | |
| **BLEEDING (ml).** | | | |
| **UNITS OF BLOOD TRANSFUSED** | | | |
| **TYPE OF BLEEDING** | | **Major intraoperative bleeding)** | **At the end of the surgical intervention** |
| | 0: no bleeding (< 1mL/min) | | |
| | 1: mild (1-5 mL/min) | | |
| | 2: moderate (5-10mL/min) | | |
| | 3: severe (10-50mL/min) | | |
| | 4: very severe (> 50mL/min) | | |
| **TYPE OF HEMOSTASIS PERFORMED** | Compression | | |
| | Coagulation | | |
| | Suture | | |
| | Application of hemostatic agent | | |
| | Name of hemostatic | | |
| **CLAMPING TIME (min)** | | | |

# ANNEX V. PATIENT INFORMATION DOCUMENT AND INDIVIDUAL INFORMED CONSENT.

## PATIENT INFORMATION DOCUMENT

**Title:** VALIDATION OF THE VIBe INTRAOPERATIVE BLEEDING SCALE IN LIVER SURGERY. PROSPECTIVE AND MULTICENTRIC STUDY.

**Promoter:** Aragon Institute for Health Research (IIS Aragon)

**Principal researcher:** Daniel Aparicio López **/** Mario Serradilla Martin / José Manuel Ramia Ángel**.**

**Tfno:** +34 697768059 **e-mail:** dani_9_93@hotmail.com / daparicio@salud.aragon.es

**Centro:** General and Digestive Surgery Department. Miguel Servet University Hospital. Zaragoza. Spain

**1. Introduction:**

We are writing to you to request your participation in a research project that we are carrying out at NAME OF THE COLLABORATING HOSPITAL. Your participation is voluntary, but it is important to obtain the knowledge we need. This project has been approved by the Ethics Committee, but before making a decision it is necessary that:

- read this entire document
- understand the information contained in the document
- ask all the questions you consider necessary
- make a thoughtful decision
- sign the informed consent, if you finally want to participate.

If you decide to participate, you will be given a copy of this sheet and the signed consent document. Please keep it in case you need it in the future.

**2. Why are you being asked to participate?**

Your collaboration is requested because you suffer from a disease that affects the liver and for its treatment requires a surgical intervention. This intervention consists of the resection of the affected liver tissue.

A total of 259 patients with these characteristics will participate in the study.

**3. What is the purpose of this study?**

With the following study, we intend to register for subsequent analysis the number of liver resections performed in 10 centers of moderate-high volume (reference centers) in Spain with the intention of determining intraoperative bleeding and validating the VIBe scale in liver surgery. Furthermore, we intend to determine the repeatability, reproducibility and usefulness of said scale in this type of surgery; and the relationship between the type of bleeding and the hemostatic agent used. There is no validated scale in liver surgery on intraoperative bleeding in the literature, and with this registry we intend to obtain them.

**4. What do I have to do if I decide to participate?**

You do not have to do anything to participate in this registry. You will not be subjected to any diagnostic test outside of the usual ones during your diagnostic and therapeutic process. It only authorizes us to quantify and record intraoperative bleeding at two moments of the surgical intervention (the moment of greatest bleeding and at the end of the surgery). Likewise, your medical history will be reviewed to collect the necessary data on the possible complications that you may suffer throughout the process. You do not have to go to more visits than usual nor will you be asked to carry out any type of survey.

**5. What risks or annoyances does it entail?**

Participation in this registry will not suppose any type of risk or additional annoyance for the patient.

**6. Will I get any benefit from my participation?**

As it is a research study aimed at generating knowledge, it is not likely that you will obtain any benefit from your participation, although you will contribute to scientific advancement and social benefit.

You will not receive any financial compensation for your participation.

**7. How will my personal data be processed?**

Responsible for the treatment: Study coordinator. Daniel Aparicio López

Purpose: Your personal data will be processed exclusively for the research work referred to in this document.

Legitimation: The treatment of the data of this study is legitimized by your consent to participate.

All the information collected will be treated in accordance with the provisions of current legislation on the protection of personal data. Personal data will not be included in the study database: neither your name, nor your medical history number nor any information that can

identify you. You will be identified by a code that only the research team will be able to associate with your name.

Only the research team will have access to the data in your medical history and no one outside the center will be able to consult your history.

In accordance with the provisions of the data protection legislation (RGPD 2016/679), you can exercise the rights of access, modification, opposition and cancellation of data. You can also limit the processing of data that are incorrect, request a copy or transfer to a third party (portability) the data that you have provided for the study. To exercise your rights, contact the principal investigator of the study. You also have the right to contact the Data Protection Agency if you are not satisfied.

If you decide to withdraw your consent to participate in this study, no new data will be added to the database, but those that have already been collected will be used. In case you want both the data and the samples already collected to be destroyed, you must expressly request it and your request will be attended to.

The coded data can be transmitted to third parties and to other countries but in no case will they contain information that can directly identify you, such as name and surname, initials, address, social security number, etc. In the event that this assignment occurs, it will be for the same purposes of the study described or for use in scientific publications but always maintaining their confidentiality in accordance with current legislation.

The promoter / researcher will adopt the pertinent measures to guarantee the protection of their privacy and will not allow their data to be crossed with other databases that could allow their identification or that they are used for purposes unrelated to the objectives of this investigation.

The conclusions of the study will be presented in conferences and scientific publications, but they will always be made with grouped data and nothing that can identify it will ever be disclosed.

**8. Who finances the study?**

This study is funded by the Investigator Initiated Research (IIR) grant from Baxter S.L.

**9. Will I be informed of the results of the study?**

You have the right to know the results of this study, both the general results and those derived from your specific data. You also have the right not to know such results if you wish. For this reason, in the informed consent document we will ask you which option you prefer. In case you want to know the results, the researcher will send you the results.

**Can I change my mind?**

Your participation is completely voluntary, you can decide not to participate or withdraw from the study at any time without having to give explanations and without this having an impact on your

health care (only for projects in the healthcare field). Simply state your intention to the study's principal investigator.

**What happens if I have any questions during my participation?**

The first page of this document contains the name and contact telephone number of the researcher responsible for the study. You can contact him if you have any questions about your participation.

Thank you very much for your attention, if you finally wish to participate, please sign the attached consent document.

## INFORMED CONSENT DOCUMENT

**Title: VALIDATION OF THE VIBe INTRAOPERATIVE BLEEDING SCALE IN LIVER SURGERY. PROSPECTIVE AND MULTICENTRIC STUDY.**

Me, ..... ..... (name and surname of the participant)
I have read the information sheet that has been provided to me.
I have been able to ask questions about the study and have received enough information about it.
I have spoken with: ..... ..... (name of researcher)
I understand that my participation is voluntary.
I understand that I can withdraw from the study:

1) whenever you want
2) without having to explain
3) without this affecting my medical care

I freely give my consent to participate in this study and I give my consent for the access and use of my data as stipulated in the information sheet that has been given to me (and for the genetic analysis to be carried out –if applicable-).

I wish to be informed about the results of the study: yes no (check all that apply)

I give my consent for my clinical data to be reviewed by personnel outside the center, for the purposes of the study, and I am aware that this consent is revocable.

I have received a signed copy of this Informed Consent.

Participant signature:

Date:

I have explained the nature and purpose of the study to the named patient

Investigator's Signature:

Date: