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Original article

Clinical mortality risk factors of variceal upper gastrointestinal bleeding in a Malagasy surgical intensive care unit

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A R T I C L E   I N F O

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A B S T R A C T

Background: Variceal upper gastrointestinal bleeding is a dreadful complication of portal hypertension with a significant morbidity and mortality. Different prognostic scores can be used. However, in the local context of Madagascar, the completion of paraclinical investigations can be delayed by the limited financial means of patients. Hence, determining clinical mortality risk factors of variceal upper gastrointestinal bleeding could be interesting. The aim of the study was to evaluate the clinical mortality risk factors of variceal gastrointestinal bleeding (VUGIB).

Method: An observational, cohort retrospective study was conducted over an 8-year period (2010–2017), at the surgical intensive care unit of the J.R. Andrianavalona University Hospital, Antananarivo, in patients admitted for VUGIB confirmed by upper gastrointestinal endoscopy and whose clinical examination was performed at admission. The primary endpoint was intensive care unit (ICU) mortality. Univariate analysis and multivariate logistic regression analysis were performed to identify risk factors for ICU mortality, with OR defining odds ratio. A p value < 0.05 was considered significant.

Results: 1920 patients were admitted for gastrointestinal bleeding of any digestive causes; the source of bleeding was variceal in 269 patients (14%). The predominantly male population (sex ratio = 2.5), aged 47.1 ± 13.7 years was mostly American Society of Anesthesiologists (ASA) 1 classification (58.4%). In 56.5% of patients, the gastrointestinal bleeding had not occurred before. The mortality rate was 16.0%. Three major clinical factors of mortality were identified: previous endoscopic band variceal ligation (OR = 12.57 [2.18–72.58], p = 0.005), tachycardia > 120 bpm (OR = 2.91 [1.04–8.14], p = 0.041), and ascites (OR = 3.80 [1.85–7.81], p < 0.001).

Conclusion: Upper gastrointestinal bleeding may be life-threatening. The mortality scores are certainly useful; however, the identification of clinical factors is interesting in countries like Madagascar, pending the results of paraclinical investigations.

African relevance

- With poor access to intensive care settings in low- and middle-income countries, admissions should include assessment of morbidity and mortality risk.
- In Madagascar, paraclinical investigations are often delayed or unavailable.
- Clinical factors could be introduced to the management process to assess morbidity and mortality risk.

Introduction

Variceal upper gastrointestinal bleeding (VUGIB) is a dreaded complication of portal hypertension [1,2]. The morbidity and the mortality remain high, and can be assessed by different scores combining clinical, biological and endoscopic parameters [1,2]. In Madagascar, 8.21% to 46% of gastrointestinal bleeding is due to ruptured esophageal varices [3,4]. Portal hypertension causes 15.38% deaths and cirrhosis, 22.73% [5].

In the local context, because of the limited financial means of many

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patients, biological and endoscopic investigations are not always all carried out in time to establish recommended prognostic scores (Child Pugh, MELD scores, …), therefore to assess morbidity and mortality of VUGIB. As clinical examination is always performed, to estimate mortality with clinical parameters seems to be more interesting. The hypothesis of the present study is that “clinical factors can predict the mortality of VUGIB in the intensive care unit”. Hence, the aim of the study was to assess the clinical mortality factors of VUGIB, in the surgical intensive care unit of a Malagasy hospital (Antananarivo).

Methods

An observational, retrospective cohort study was carried out in the surgical intensive care unit (SICU) of the JR Andrianavalona University Hospital Center (Centre Hospitalier Universitaire Joseph Ravoahangy Andrianavalona, CHU JRA), over a period of eight years, from 2010 to 2017. Anesthesiologist intensivist physician runs this unit which is mainly composed of intensivists and physician assistants. This SICU size is forty beds capacity with nearly 1500 to 2500 admissions per year. Admitted patients in SICU are those from the emergency department, from the other surgical and oncologic units, and from operating room of the CHU JRA. The patients (adults and pediatric patients) requiring close monitoring and/or vital functions support are hospitalized in SICU. Also, patients with gastrointestinal (GI) bleeding (upper or lower, variceal or not) are admitted in SICU, when therapeutic management in the emergency department or in the other units fails. The emergency department (ED) is headed by an anesthesiologist intensivist physician and is composed of emergency physicians, anesthesiologist intensivist physicians, and assistant physicians. This ED has an ‘emergency-triage-reception’ section (where patients are taken care of upon arrival at hospital) and a resuscitation sector where unstable and postoperative patients of emergency surgeries are admitted before transfer to the surgical sectors or in surgical resuscitation, according to the patient’s condition.

For this study, the records of patients admitted for upper gastrointestinal bleeding (UGIB) have been studied. The retained patients’ files were those of patients having presented UGIB whose variceal origin was confirmed by early (in the 24 h after admission) or late gastrointestinal endoscopy (during or after SICU hospitalization), and whose clinical parameters on admission to intensive care unit were all available. The main outcome was the ICU mortality of variceal upper gastrointestinal bleeding during the length of stay in SICU (CHU JRA).

Statistical analyzes were carried out with SigmaPlot® 10.0 software. A simple descriptive analysis was carried out on the entire study population. This description focused on patients’ parameters (age, gender, ASA [American Society of Anesthesiologists] physical status classification), data relating to VUGIB (bleeding presentation, bleeding episode), patient’s medical history, physical examination parameters and outcome of the patients. Results are expressed as mean ± standard deviation (for continuous variables) or as a percentage (for categorical variables). A univariate analysis was performed to determine the clinical factors associated with VUGIB mortality before including them in a multivariate analysis. These clinical factors were collected and grouped from patient data records. The statistical tests used were correlation and multiple logistic regression tests. The correlation test was done in order to study the correlations between clinical parameters and mortality of VUGIB; the correlation coefficient is defined by R. To assess the clinical mortality factors of VUGIB in SICU (CHU JRA), multivariate analysis by multiple logistic regression was performed to estimate the Odds Ratio (OR) with confidence interval at 95% (CI 95) for each retained factor (conservative threshold 0.20). The significance threshold was set at 0.05 and all the tests were two-sided.

Results

Of the 19,198 admissions to surgical intensive care unit during the study period, 1920 patients were admitted for gastrointestinal hemorrhage (upper or lower, variceal or not). Among them, 269 patients presented UGIB caused by esophageal and/or gastric varices (Fig. 1). The male-dominated study population (sex ratio = 2.5) was
### Table 1
Population characteristics and medical story.

|                      |  N   | %     |
|----------------------|------|-------|
| **Age (years)**      |      |       |
| < 30                 | 22   | 8.2   |
| [30-60]              | 185  | 68.8  |
| > 60                 | 62   | 23.0  |
| **Gender**           |      |       |
| Men                  | 192  | 71.4  |
| Women                | 77   | 28.6  |
| **ASA classification** |    |       |
| I                    | 157  | 58.4  |
| II and more          | 112  | 41.6  |
| **Prior betablocker therapy** | 23 | 8.5 |
| **Previous variceal upper gastrointestinal bleeding** | 14 | 5.2 |
| **Previous variceal band ligation** | 62 | 23.0 |
| **Previous pathologies** |   |       |
| Alcoholism           | 81   | 30.1  |
| Schistosomiasis      | 16   | 5.9   |
| Cirrhosis            | 13   | 4.8   |
| Acites               | 10   | 3.7   |
| Spleenectomy         | 5    | 1.9   |
| Hepatitis            | 5    | 1.9   |
| Jaundice             | 2    | 0.7   |

ASA (American Society of Anesthesiologists) physical status classification.

### Table 2
Presentation of the GI bleeding and clinical examination.

|                       |  N   | %     |
|-----------------------|------|-------|
| **Bleeding presentation** |    |       |
| Hematemesis           | 85   | 31.6  |
| Hematemesis and melena | 151  | 56.1  |
| Melena                | 33   | 12.3  |
| **Bleeding episode**  |      |       |
| First episode         | 152  | 56.5  |
| Two or more episodes  | 117  | 43.5  |
| **Clinical signs at admission** |   |       |
| Splenomegaly          | 134  | 49.8  |
| Ascites (clinically assessable) | 81 | 30.1 |
| Splenomegaly and hepatomegaly | 26 | 9.7 |
| Hepatomegaly          | 21   | 7.8   |
| Jaundice              | 12   | 4.5   |
| Abdominal collateral venous circulations | 7 | 2.6 |
| Leg edema             | 6    | 2.2   |
| Consciousness disorders | 4   | 1.5   |
| **Arterial blood pressure** |   |       |
| Heart rate (bpm)      |      |       |
| < 80                  | 52   | 19.3  |
| 80–100                | 119  | 44.2  |
| 100–120               | 76   | 28.2  |
| > 120                 | 22   | 8.2   |

Splenomegaly with Hackett grading system ≥ 2.

### Table 3
VUGIB characteristics and patient's history associated to mortality.

|                        | Survival (n) | Death (n) | R     | p   |
|------------------------|--------------|-----------|-------|-----|
| **Bleeding presentation** |              |           |       |     |
| Hematemesis            | 71           | 14        | 0.021 | 0.73|
| Hematemesis and melena | 129          | 22        | 0.021 | 0.73|
| Melena                 | 26           | 7         | 0.021 | 0.73|
| **Bleeding episode**   |              |           |       |     |
| First episode          | 116          | 36        | −0.239| 0.000074|
| Second or more episode | 110          | 7         | 0.021 | 0.73|
| **Medical history of VUGIB** |         |           |       |     |
| Previous VUGIB         | 46           | 5         | 0.084 | 0.17|
| EVL                    | 9            | 5         | 0.126 | 0.034|
| Prior betablocker therapy | 18       | 5         | 0.047 | 0.438|
| **Previous pathologies** |            |           |       |     |
| Alcoholism             | 49           | 13        | 0.0545| 0.41|
| Prior schistosomiasis  | 15           | 1         | −0.067| 0.27|
| Previous cirrhosis     | 11           | 2         | −0.004| 0.95|
| Previous ascites       | 7            | 3         | 0.088 | 0.15|
| Previous splenectomy   | 4            | 1         | 0.015 | 0.81|
| Previous hepatitis     | 4            | 1         | 0.015 | 0.81|
| Previous jaundice      | 1            | 1         | 0.080 | 0.18|

Significant results are in bold (p < 0.05).
Not significant results are in italics (p ≥ 0.05).

### Table 4
Clinical parameters associated to mortality.

|                       | Survival (n) | Death (n) | R     | p   |
|-----------------------|--------------|-----------|-------|-----|
| Physical signs at the admission in SICU |              |           |       |     |
| Splenomegaly          | 120          | 14        | −0.151| 0.013|
| Ascites               | 58           | 23        | 0.222 | 0.000024|
| Hepatomegaly & splenomegaly | 22   | 4       | −0.013| 0.83|
| Hepatomegaly          | 18           | 3         | −0.039| 0.52|
| Jaundice              | 10           | 2         | 0.004 | 0.95|
| Collateral venous circulations | 5       | 2       | 0.056 | 0.36|
| Leg edema             | 4            | 2         | 0.056 | 0.36|
| Consciousness disorders | 2       | 2       | 0.114 | 0.0644|
| Systolic arterial blood pressure (mm Hg) |              |           |       |     |
| Unrecordable          | 5            | 6         | 0.217 | 0.0000331|
| < 90                  | 31           | 8         | 0.515 | 0.41|
| 90 to 130             | 27           | 180       | −0.147| 0.0161|
| > 130                 | 10           | 2         | 0.004 | 0.95|
| Diastolic arterial blood pressure (mm Hg) |              |           |       |     |
| Unrecordable          | 5            | 6         | 0.217 | 0.000331|
| < 60                  | 9            | 1         | −0.032| 0.6000|
| 60 to 70              | 174          | 31        | −0.042| 0.49|
| > 70                  | 38           | 5         | −0.052| 0.40|
| Heart rate (HR) (bpm) |              |           |       |     |
| < 80                  | 44           | 8         | 0.008 | 0.89|
| 80 to 100             | 106          | 13        | −0.123| 0.0438|
| 100 to 120            | 63           | 13        | 0.019 | 0.75|
| > 120                 | 13           | 9         | 0.203 | 0.0000813|
| Calculated shock index (HR/ SBP) |              |           |       |     |
| < 1                   | 143          | 23        | 0.059 | 0.34|
| ≥ 1                   | 83           | 20        |       |     |

Significant results are in bold (p < 0.05).
Not significant results are in italics (p ≥ 0.05).

* Surgical intensive care unit.
* Abdominal localization.

47.1 ± 13.7 years old. Most of patients were ASA I (58.4%). Fifty-one patients (18.9%) had a history of esophageal varices (EV) diagnosed during a previous endoscopy; and 14 patients (5.2%) had endoscopic variceal band ligation (EVL) for esophageal varices (Table 1). In the medical history of patients, alcoholism (23.0%) was the most found and schistosomiasis in 5.9% (Table 1). The bleeding presentations were mostly hematemesis associated with melena (56.1%) (Table 2).

During physical examination at admission in SICU, the hemodynamic parameters were as follows: the systolic blood pressure (SBP) was 99 ± 27 mm Hg, the diastolic blood pressure (DBP) was 54 ± 17 mm Hg. The heart rate (HR) was 94 ± 18 bpm. The calculated shock index (HR/SBP) was 0.9 ± 0.2. Splenomegaly (49.8%) and ascites (30.1%) (Table 2) were the most observed clinical signs.

Forty-three patients (16% of mortality) died after 3.9 ± 4.8 days of stay in SICU. Mortality was related to the number of bleeding episodes on admission and not to the presentation of VUGIB (Table 3).

Patients with melena had significant higher mortality. Bleeding episode had a negative correlation with SICU mortality: for patients who were admitted to intensive care because of a second - or more - bleeding episode, the mortality was lower (Table 3).

Regarding hemodynamic parameters, systolic and diastolic as well as heart rate were associated with mortality (Table 4) and among them, the heart rate was the only independent factor of mortality (OR = 1.88).
Table 5
Independent clinical factors of mortality.

| Factor                                    | OR    | 95% CI | p     |
|-------------------------------------------|-------|--------|-------|
| Bleeding episode                          |       |        |       |
| Second or more episode                    | 0.20  | 0.09–0.48 | < 0.001 |
| Medical history of VUGIB                  |       |        |       |
| Previous VUGIB                            | 0.19  | 0.04–0.81 | 0.025 |
| Endoscopic varical band ligation          | 12.57 | 2.18–72.58 | 0.005 |
| Prior beta-blocker therapy                | 1.51  | 0.53–4.32 | 0.439 |
| Medical history                           |       |        |       |
| Previous ascites                          | 2.79  | 0.728–11.646 | 0.16 |
| Previous jaundice                         | 1.72  | 0.942–91.251 | 0.23 |
| Physical signs                            |       |        |       |
| Ascites                                   | 3.80  | 1.85–7.81 | < 0.001 |
| Splenomegaly                              | 0.39  | 0.18–0.83 | 0.015 |
| Consciousness disorders                   | 4.36  | 0.53–36.04 | 0.17 |
| Hemodynamic parameters                    |       |        |       |
| Unrecordable blood pressure               | 3.59  | 0.85–15.20 | 0.08 |
| SBP ≥ 90 to 130 mm Hg                     | 0.61  | 0.27–1.38 | 0.24 |
| HR ≤ 80 to 100 bpm                        | 0.64  | 0.30–1.37 | 0.25 |
| HR > 120 bpm                              | 2.91  | 1.04–8.14 | 0.041 |

Significant results are in bold (p < 0.05).
Not significant results are in italics (p ≥ 0.05).
* Variceal upper gastrointestinal bleeding.
* Systolic arterial blood pressure.
* Heart rate.

Discussion

The mortality from VUGIB, in surgical intensive care unit of the CHU JRA was 16%. The three major clinical risk factors are a history of endoscopic varical band ligation (EVL), ascites at clinical examination and a heart rate greater than or equal to 120 bpm, increasing the risk of death by 12.57 times, 3.80 times and 2.91 times respectively. The mortality of the present study is similar with those found in other studies, between 8.6 and 30% [2,6–8]. However, this should be interpreted with caution because our study is about ICU mortality.

The usual risk factors of VUGIB are rebleeding, bleeding during upper gastrointestinal endoscopy, high Child-Pugh and MELD scores [1,6–8]. The endoscopic risk factor is difficult to consider in the local context, because it is not always performed at the admission. Moreover, the Child-Pugh score as well as MELD score require biological parameters (blood albumin level, prothrombin level, blood creatinine level) which are not always performed for all patients on admission in SICU or later. Thus, the assessment of mortality risk factors from the clinical examination appears more relevant in the context of Antananarivo - Madagascar. The clinical risk factors for mortality found by other authors are ascites, jaundice, hepatic encephalopathy, alcoholic liver disease and shock (without being constant) [6–8]. Komori et al. [9] found that the “classical” factors of mortality were not associated with the mortality from VUGIB; except hepatocarcinoma (increases mortality by 5.17 [p = 0.02091]). Jaundice and hepatic encephalopathy were not correlated with mortality in our study. Only ascites was the common factor of mortality as found by some authors, like Jairath V et al. [6] (OR = 4.18) and Mouelhi L et al. [8]. It was found in the present results that the history of endoscopic varical band ligation (EVL) is a factor of mortality from VUGIB. In Antananarivo, EVL is performed in another hospital and are mostly realized after discharge from SICU. Furthermore, the EVL was recently established in Antananarivo (around 2015), and patients before 2015 did not benefit from it. Thus, EVL interpretation could be a risk of bias in the results. The variceal band ligation is known as a means of reducing recurrence and mortality from VUGIB. Carbonnel N et al. [10] find a 3-fold decrease in mortality in 20 years, after early achievement of an EVL, from 42.5% to 14.5%. Indeed, the EVL allows the eradication of esophageal varices (EV) from 62.5% to 73.8% [11,12]. The relation between EVL and mortality in our study would probably be linked to the fact that concomitant vasoactive treatment for VUGIB (somatostatin, octreotide) is not carried out, due to its unavailability, in Antananarivo - Madagascar. Indeed, the early prescription of a vasoactive treatment, associated with endoscopic treatment, allows better hemostasis by its early action, in VUGIB and this association is more effective than EVL alone or the treatment vasoactive alone [13–15]. Bassène ML et al. [16], in Senegal, report endoscopic control of the bleeding, with 2 to 3 ligation sessions spaced four weeks on average, despite the unavailability of vasoactive drugs. In our study, the completion time and the number of EVL sessions were not determined; which could also have presented a bias for the found results.

An elevated heart rate is not always considered a factor in mortality. Jairath V et al. [6] and Chaikitamuaychok R and Patumanond J [17] find that a tachycardia of > 100 bpm is correlated with the severity of the gastrointestinal hemorrhage and also constitutes a factor of mortality (×1.72) for VUGIB. Tachycardia is most often associated with a low systolic blood pressure characterizing a state of shock, which multiplies the mortality of VUGIB up to 4.55 [6,17–19]. However, this factor cannot be a severity and/or mortality factor in VUGIB, as found by Moledina SM and Komba E [20].

These clinical mortality factors must be interpreted with consideration of the local context. Indeed, the etiologies of VUGIB are mainly represented by alcoholism and schistosomiasis. Bilharziasis or hepatic schistosomiasis is a non-cirrhotic cause of portal hypertension; it is an endemic disease in Madagascar [21,22]. Being chronic, portal hypertension appears. Also, when splenomegaly is bulky it often leads to hypersplenism [21,23]. In our study, neither the stage of splenomegaly nor the degree of splenic sequestration was evaluated; the fact that this variable seems to be a protective factor may lack specificity. This can be explained by the fact that schistosomiasis is endemic in Madagascar; splenomegaly is chronic and common even in the absence of portal hypertension [23,24]. About the bleeding episode, we found that when the VUGIB occurs more or equal to two times, an OR less than 1 (OR < 1) was found. Probably, the first episode may represent a massive hemorrhage and lead to further mortality. Indeed, VUGIB in its inaugural/first episode is associated with significant morbidity and mortality (30 to 66%); the existence of previous bleeding episodes does not appear to be independent prognostic factors [25,26]. In addition, beta-blocker therapy is often prescribed for EVs; the effect of beta-blockers is substantial when faced with large or medium varicose veins or whose hepatic pressure gradient is > 12 mm Hg [27]. Betablockers allow the prevention of hemorrhage and a reduction in mortality in cirrhotic patients [27,28]. That may explain the fact that the second or more bleeding episode could be a “protective factor” of mortality in VUGIB although prior beta-blocker therapy is not correlated with mortality in the present study.

The strength of our study is the assessment of clinical mortality risk factors in a large Malagasy population; above all, when patients cannot financially support the expenses related to the realization of biological assessments. However, this study is limited by its monocentric characteristic and by the lack of comparison with conventional mortality scores. In addition, UGIB may have caused organ failure, which was not assessed in our study and therefore may tend to bias our results.

Conclusion

The burden of VUGIB is significant in this setting contributing to a high mortality rate of 16% (3.9 ± 4.8 days). Associated risk factors
and mortality risk factors of VUGIB include a history of endoscopic variceal band ligation, a heart rate > 120 bpm and the presence of ascites. Early identification of at least one of these factors in the emergency department or on admission would allow improved identification of patients at high-risk and potentially optimize their therapeutical management.

Dissemination of results

Results from this study were shared with the National Anesthesia and Intensive Care Society (Société d’Anesthésie Réanimation de Madagascar).

Authors’ contribution

Authors contributed as follow to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content: AR contributed 40%; NMMP 25%; FS 15%; HMR 12.5%; JGR 7.5%; and RMR and ATR contributed 5% each. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Declaration of competing interest

The authors declared no conflicts of interest.