Gastrointestinal Bleeding in Patients Who Underwent HeartMate 3 Left Ventricular Assist Device Implantation

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ABSTRACT **Background:** Continuous-flow left ventricular assist devices (CF-LVADs) have yielded improved outcomes compared with pulsatile-flow devices; however, significant rates of gastrointestinal bleeding (GIB) have been observed. The HeartMate 3 left ventricular assist device (HM3-LVAD) (Abbott, Inc., Chicago, IL, USA) includes new features, such as an artificial pulse, which may decrease GIB prevalence compared to the HeartMate 2 left ventricular assist device (HM2-LVAD).

Objectives: To evaluate the incidence, predictors, and clinical outcomes of GIB in patients supported by the HM3-LVAD.

Methods: From 2016 until 2024, 180 patients with chronic heart failure underwent HM3-LVAD implantation. Records were reviewed to determine the post-implant GIB prevalence, location of the bleeding, and associated morbidity and mortality. Univariate and multivariate analyses were conducted to identify independent predictors of GIB.

Results: GIB occurred in 25 patients (14%) with a duration of support ranging from 1 to 1821 days. Sources of GIB included the small bowel and rectum in eight patients each, large bowel in one, and stomach in two. No clear source was identified in 11 patients. Recurrent GIB occurred in 16 patients (64%). There were no deaths attributable to GIB. None of the historical or demographic parameters were found to be independent predictors of GIB.

Conclusions: GIB is a frequent source of morbidity for patients on HM3-LVAD support but does not significantly impact survival. As the implantation of CF-LVADs with non-pulsatile flow gains popularity for both bridge-to-transplant and destination therapy, a better understanding of the pathophysiology of GIB in these patients will reduce the prevalence of this complication.

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KEY WORDS: gastrointestinal bleeding (GIB), left ventricular assist device (LVAD), HeartMate 3 (HM3)

The frequency of fully magnetically levitated centrifugal-flow HeartMate 3 Left Ventricular Assist Device (HM3-LVAD) (Abbott, Inc., Chicago, IL, USA) implants among patients with end-stage heart failure has increased greatly over recent years [1-3]. The most common complications of LVAD implantation include infection, cerebral vascular accident (CVA), and gastrointestinal bleeding (GIB). One strategy to reduce GIB has been the development of pulsatile-flow devices. These devices have been associated with improved outcomes and reduced GIB prevalence in patients receiving long-term support. The HM3-LVAD features an artificial pulse, which may reduce GIB prevalence compared to the HeartMate 2 (HM2-LVAD) [4-7].

The mechanism of GIB in left ventricular assist device (LVAD) patients is not yet fully understood. However, several possible mechanisms, including arteriovenous malformation formation, impaired platelet aggregation, and acquired von Willebrand Syndrome, are suspected of contributing [8]. In this study, we present the incidence and predictors of postoperative GIB in patients who underwent HM3-LVAD implantation.

Both replacement coagulation approaches [9] and the addition of pulsatility to continuous-flow LVADs (CF-LVADs) have been investigated in efforts to reduce postoperative GIB rates. While coagulation factor replacement strategies have not significantly reduced postoperative GIB, newer devices such as the HM3, which introduces artificial pulsatility, have shown promise. Compared to older CF-LVADs like the HeartMate 2 and HeartWare (HVAD), the HM3's pulsatile design may help reduce the incidence of GIB. Introducing pulsatility into LVADs helps maintain more physiologic vascular dynamics and may reduce the formation of arteriovenous malformations. In addition,

pulsatility reduces shear stress on the vasculature and mitigates the degradation of von Willebrand factor seen with non-pulsatile LVADs.

This study represents one of the largest single-center evaluations of GIB in HM3-LVAD patients with extended follow-up. By examining recurrence patterns, anticoagulation management, and prognostic markers such as C-reactive protein (CRP) and extracorporeal membrane oxygenation (ECMO) status, it offers novel insights into risk stratification and therapeutic decision-making in this population.

PATIENTS AND METHODS

STUDY DESIGN

This single-center retrospective analysis of all patients who underwent HM3-LVAD implantation at Sheba Medical Center between January 2016 and January 2024 included those with concomitant procedures. We collected and compared preoperative, intra-operative, and postoperative characteristics, as well as short-term and medium-term mortality rates, between GIB and non-GIB groups. Data were collected from the Sheba Medical Center Cardiac Surgery Clinical Database. This study was approved by the institutional review board (IRB 4527). Due to the retrospective design, the review board waived the requirement to obtain patient consent.

PATIENT DATA

Preoperative characteristics included age, sex, body mass index, and etiology of heart failure (e.g., ischemic cardiomyopathy, dilated cardiomyopathy, and peripartum cardiomyopathy). Co-morbidities included hypertension, diabetes mellitus, smoking history, chronic obstructive pulmonary disease (COPD), cardiac surgery history, ischemic heart disease, chronic renal insufficiency, CVA, ECMO, myocarditis, and peripheral vascular disease. Treatment plans included bridge-to-transplant versus destination therapy and Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs) level.

Preoperative and postoperative lab tests included hemoglobin, platelets, creatinine, liver function tests, total bilirubin, albumin, and international normalized ratio (INR). Hemodynamic and echocardiographic data included preoperative and follow-up assessments, such as left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), mitral regurgitation/insufficiency, tricuspid regurgitation/insufficiency, aortic valve regurgitation/insufficiency, central venous pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, and cardiac index.

Intra-operative characteristics included device type (HM3-LVAD), cardiopulmonary bypass time, and concomitant surgical procedures. Postoperative characteristics included 30-day, 6-month, and 12-month mortality rates, as well as complications such as reoperation for bleeding, infection, CVA, respiratory failure, acute renal failure, GIB, right ventricular (RV) failure, and pump thrombosis. RV failure was defined as the need for inotropic support for more than one week or right ventricular assist device (RVAD) support [10,11]. Acute renal failure was defined as a glomerular filtration rate of < 60 ml/min/m² [12,13]. GIB was defined as a hemoglobin drop > 1 g/dl accompanied by one or more of the following: positive guaiac stool test, melena, hematemesis, or active bleeding observed during endoscopic evaluation (upper or lower). Bleeding location was determined via colonoscopy, capsule endoscopy of the small bowel, or esophagogastroduodenoscopy.

GASTROINTESTINAL BLEEDING DETECTION AND REPORTING

All suspected gastrointestinal bleeding (GIB) events were prospectively recorded in the institutional LVAD registry. Events were defined as a hemoglobin drop of > 1 g/dl accompanied by overt bleeding, positive stool guaiac test, or visualization of bleeding on endoscopy. Follow-up documentation, visits to our heart failure clinic, and hospital readmissions were screened to ensure that all gastrointestinal bleeding events were obtained.

POST-IMPLANTATION ANTICOAGULATION AND ANTIPLATELET MANAGEMENT

The standard post-implant regimen consisted of warfarin (target INR 2.0–3.0) and aspirin 81 mg/day. It was initiated within 48 hours post-surgery after hemostasis was achieved. Warfarin dosing was adjusted in the heart failure clinic and primary care physicians with weekly INR monitoring. However, there were six patients who had recurring gastrointestinal bleeding and were treated with a different anticoagulant therapy.

PREOPERATIVE GASTROINTESTINAL EVALUATION

Routine preoperative gastrointestinal screening, including upper endoscopy and colonoscopy, was not systematically performed during the study period. These evaluations were conducted at the discretion of the treating cardiology or cardiac surgery teams, primarily in patients with a history of prior gastrointestinal symptoms or bleeding.

STATISTICAL ANALYSIS

Continuous variables are presented as mean ± standard deviation or median when the variance was high. A Cox proportional hazards regression analysis was performed to assess the association between survival time and several clinical factors among patients undergoing HM3-LVAD implantation. The primary model included patients who had GIB vs. non-GIB, smoking history, hypertension, diabetes mellitus, COPD, or previous cardiac surgery as covariates. A secondary model was developed to explore additional variables, including ischemic heart disease, coronary artery disease, INR, GIB, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin, platelets, CRP, ECMO use, and atrial fibrillation (AFib).

Statistical analyses were performed using R Statistical Software, version 2023.09.1+494 (R Foundation for Statistical Computing, Vienna, Austria). Key objectives, including survival, were used for survival analysis, visualization, and the generation of regression tables. A significance threshold of $P < 0.05$ (two-sided) was applied to determine statistical significance. Missing data were retained using *not available* categories to preserve cohort size in multivariate analyses. The Cox regression model estimated hazard ratios (HRs) with 95% confidence intervals and corresponding *P*-values for each variable. A global test of the Cox model was performed to evaluate the overall predictive power of all covariates within each model.

RESULTS

CHARACTERISTICS OF GIB VS. NON-GIB PATIENTS

During the study period, 180 adult patients underwent HM3-LVAD implantation. The mean age was 57 years in the non-GIB group and 62 years in the GIB group. The non-GIB group included 123 (79%) males and 32 (21%) females. The GIB group consisted of 23 (92%) males and 2 (8%) females [Table 1]. Of the 180 patients, 25 presented with postoperative GIB. Comparisons of demographics and preoperative characteristics for these sub-groups are outlined in Table 1. Significant differences were noted in age, AST, ALT, creatinine, albumin, CRP, and hemoglobin.

POSTOPERATIVE COMPLICATION RATES

Postoperative complication rates were similar, with no significant differences between the GIB and non-GIB groups [Table 2].

Table 1. Baseline demographics and preoperative characteristics

Variable	Non-GIB (n=155)	GIB (n=25)	*P*-value
Age in years	57	63	0.00
Male	123 (79%)	23 (92%)	0.33
Female	32 (21%)	2 (8%)	0.33
Previous cardiac surgery	38 (25%)	5 (20%)	0.85
Previous ECMO	55 (35%)	3 (12%)	0.07
Smoking history	76 (29%)	18 (72%)	0.15
Hypertension	72 (46%)	15 (60%)	0.54
COPD	8 (5%)	4 (16%)	0.15
Diabetes mellitus	65 (42%)	16 (64%)	0.16
CAD	77 (50%)	19 (76%)	0.07
CVA/TIA	23 (15%)	6 (24%)	0.57
Chronic kidney disease	35 (23%)	7 (28%)	0.83
Bridge-to-heart transplant	110 (71%)	20 (80%)	0.65
Dilated cardiomyopathy	56 (36%)	6 (24%)	0.45
Ischemic cardiomyopathy	90 (58%)	20 (80%)	0.15
EF (%)	17	17	0.79
Aspartate aminotransferase	41	73	0.01
Alanine aminotransferase	88	31	0.00
Creatinine	1.36	1.32	0.77
Albumin	3.4	3.63	0.09
CRP	75.79	35.54	0.02
Hemoglobin	11.9	11.65	0.76
WBCs	10	10.13	0.76
Platelets	184	204	0.34
Total bilirubin	1.28	1.52	0.61
INR	1.17	1.17	0.88

COPD = chronic obstructive pulmonary disease, CAD = coronary artery disease, CRP = C-reactive protein, CVA = cerebral vascular accident, ECMO = extracorporeal membrane oxygenation, EF = ejection fraction, GIB = gastrointestinal bleeding, INR = international normalized ratio, TIA = transient ischemic attack, WBC = white blood cell count

TIMING AND CHARACTERISTICS OF GIB EPISODES

Of the 25 patients who experienced GIB, 6 (24%) presented within 30 days after implantation (early GIB) and 19 (76%) developed bleeding beyond 30 days (late GIB). The first gastrointestinal bleeding event occurred at a median of 361 days (IQR 560, range 3–1368 days) after implantation. The small bowel and rectum were the most common sources; each identified in eight patients. In 11 patients (44%), no definite source was localized despite endoscopic evaluation. Device-related variables such as

Table 2. Postoperative complications

Variable	Non-GIB (n=155)	GIB (n=25)	*P*-value
Reoperation for bleeding	11 (7%)	5 (20%)	0.15
Driveline/sternal infection	72 (46%)	14 (56%)	0.87
CVA	19 (12%)	1 (4%)	0.41
Renal failure	14 (9%)	3 (12%)	0.94
Respiratory failure	21 (14%)	3 (12%)	0.95
RV failure	10 (6%)	0 (0%)	0.39
Device technical problems	1 (1%)	0 (0%)	0.92
Thrombosis requiring exchange	3 (2%)	0 (0%)	0.76

CVA = cerebral vascular accident, GIB = gastrointestinal bleeding, RV = right ventricular

Table 3. Survival outcomes

Variable	Non-GIB (n=155)	GIB (n=25)	*P*-value
Survival 1 month	88%	100%	0.2
Survival 6 months	80%	92%	0.97
Survival 12 months	78%	92%	0.76

GIB = gastrointestinal bleeding

LVAD speed, power, and pulsatility index were not routinely documented in our registry and were therefore unavailable for comparative analysis between groups.

ANTI-COAGULATION MANAGEMENT AND RECURRENCE AFTER GIB

Aspirin and warfarin were temporarily stopped, and octreotide was initiated in all patients who presented with GIB. Sixteen patients (64%) experienced recurrent GIB. Following resolution, patients were restarted on both 81 mg/day of aspirin and warfarin. Six patients were treated with different anticoagulants. During follow-up, no thromboembolic complications were observed.

FOLLOW-UP OUTCOMES

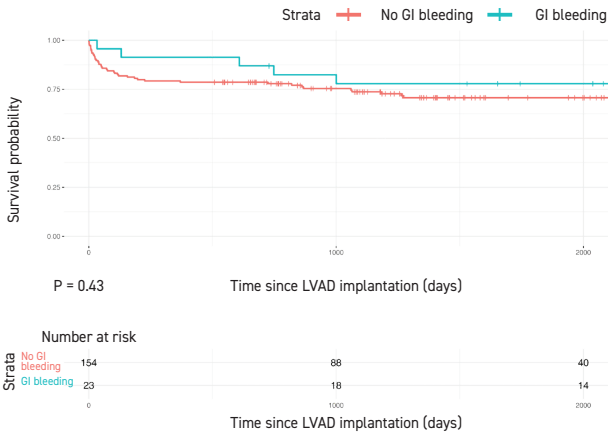
The median duration of LVAD support was 2 years (range 1 day–7.2 years). At the end of follow-up, 51 patients (28%) underwent heart transplantation, 2 (1%) were explanted, and 63 (35%) died while on support. None of the deaths were attributed to GIB.

SURVIVAL RATES OF GIB AND NON-GIB PATIENTS

Survival rates at 30 days, 6 months, and 12 months post-implantation were not significantly different between groups. The 30-day, 6-month, and 12-month survival rates were 100%, 92%, and 92% for the GIB group and 88%, 80%, and 78% for the non-GIB group, respectively ($P = 0.20$, 0.97, and 0.76) [Table 3, Figure 1].

Figure 1. Kaplan-Meier curve for survivability

GI = gastrointestinal, LVAD = left ventricular assist device



DISCUSSION

This study highlights the significant burden of GIB among HM3-LVAD recipients, with a 14% incidence in our cohort. Although our findings are consistent with prior studies [14-16], we observed no significant impact on overall survival. Nevertheless, GIB remains a major source of morbidity, emphasizing the need for improved prevention and management strategies.

Our findings support previous literature implicating that the HM3-LVAD's artificial pulse may potentially be one of the reasons for the decreased GIB rates compared to earlier devices such as the HM2 and HVAD. However, in contrast to Hammer and colleagues [17], we observed a higher recurrence rate: 64% of patients with GIB experienced more than one episode, compared to 34% reported in their study. These variances highlight the limitations of current preventive strategies.

In contrast to others who have reported 34% recurrent [17], we observed a higher rate of recurrent bleeding (64% vs 34%). This difference may reflect our longer duration of follow-up. The lower overall incidence of GIB (14%) compared with earlier continuous-flow LVAD studies (approximately 30%) may be due to advances in HM3 design and consistent anticoagulation monitoring, although underreporting of minor events cannot be excluded.

Importantly, multivariate analysis revealed that ECMO use was the strongest predictor of mortality (HR = 3.33, $P = 0.001$), suggesting that the severity of illness, rather than GIB itself, was a more critical determinant of adverse outcomes. The apparent protective association of GIB with survival (HR = 0.45, $P = 0.12$) likely represents survivor bias: the highest-risk patients supported with ECMO frequently died before living long enough to develop GIB. This finding emphasizes the need to account for ECMO status in future risk stratification models.

Interestingly, GIB was associated with a hazard ratio of 0.45, suggesting a potential protective effect, although this did not reach statistical significance ($P = 0.12$). This counterintuitive trend may reflect closer monitoring and more aggressive management in patients who experience GIB, or it may be a statistical artifact influenced by confounding variables such as ECMO. Among laboratory parameters, pre-implant CRP levels emerged as a significant predictor of mortality (HR = 1.00, $P = 0.036$), indicating that systemic inflammation may play a role in post-implant outcomes. This finding supports the potential utility of CRP as a prognostic biomarker in HM3-LVAD patients. Platelet count showed a near-significant trend ($P = 0.073$), warranting further investigation into its role in bleeding and thrombotic complications.

The absence of significant associations between survival and other variables such as smoking, diabetes, obesity, and INR suggests that traditional cardiovascular risk factors may be less relevant in this highly selected population. Rather, device-related and hemodynamic factors appear to play a more prominent role.

Finally, the high proportion of GIB cases without an identified source (44%) highlights the limitations of current diagnostic modalities. Advances in imaging and endoscopic techniques could improve the localization of bleeding sources, potentially reducing both recurrence rates and overall morbidity.

The lack of significant predictors of GIB among demographic and preoperative parameters in this study suggests that other device-specific or hemodynamic factors may contribute to its occurrence [6]. The absence of mortality directly attributable to GIB is reassuring. However, the temporary cessation of anticoagulation and adjustments in antithrombotic regimens raise concerns about thrombotic risks. Future studies should focus on optimizing anticoagulation protocols to balance bleeding and thrombotic risks effectively.

Our data also support growing evidence that temporary interruption or even permanent discontinuation of warfarin can be safe in selected HM3 recipients after resolution of GIB, corresponding with the ARIES-HM3 randomized trial [18]. No thrombotic complications were observed despite a subset of patients remaining off anticoagulation long term.

CLINICAL IMPLICATIONS

Despite the artificial pulse feature of the HM3-LVAD, GIB remains a frequent and often recurrent complication, suggesting that device design alone may not sufficiently reduce bleeding risk. Clinicians may need to adopt individualized anticoagulation protocols, especially for patients with prior GIB, elevated CRP, or ECMO history, rather than relying solely on standardized regimens. Close monitoring is essential in patients with prior GIB, given the high recurrence rate observed in our study (64%). Our observations also support the safety of temporary anticoagulation cessation in controlled settings, as no deaths were attributable to GIB. Given that 44% of GIB cases lacked a clear source, a more standardized and proactive diagnostic workup–potentially involving early capsule endoscopy–may improve outcomes and reduce recurrence.

LIMITATIONS

This study is limited by its retrospective, single-center design, which may affect the generalizability of findings. In addition, bleeding source localization was incomplete in a substantial proportion of patients, potentially limiting the precision of diagnostic outcome comparisons. While the sample size is among the largest reported for HM3-LVAD GIB, the subgroup sizes for certain analyses (e.g., recurrence) were relatively small, which may have reduced statistical power.

CONCLUSIONS

While HM3 LVADs have reduced the prevalence of GIB compared to earlier models, it remains a frequent and complex complication. Further research into the pathophysiology of GIB, improvements in device technology, and refined management protocols are essential to enhance patient outcomes.

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Capsule

TET2 mutations and immunotherapy

Loss-of-function mutations in the epigenetic regulator TET2 (Tet methylcytosine dioxygenase 2) are frequently found in myeloid cell (blood) malignancies. Impaired TET2 activity has been associated with improved tumor response to adoptive T cell–based immunotherapy, yet the underlying immune mechanisms are currently unclear. In two independent studies, **Rondeau** and colleagues and **Herbrich** and colleagues reported that genetic inactivation of TET2 in white blood cells can remodel the tumor microenvironment by priming the myeloid compartment and T cell states. In human melanoma, lung, and colon cancer cohorts, TET2 mutations corresponded with improved response to checkpoint blockade immunotherapy. These studies provide insights into how TET2 mutations in blood cells might influence solid tumor growth and treatment response.

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Capsule

Broadly neutralizing antibodies for HIV

Broadly neutralizing antibodies (bNAbs) emerge infrequently during natural HIV-1 infection and have become the focus of HIV-1 vaccine development. **Habib** and co-authors identified the V2 apex region of the HIV envelope (Env) as the most common target of bNAbs in nonhuman primates and also found a subset of Envs that preferentially elicits them. The researchers tracked the coevolution of bNAb development and the emergence of Env escape variants in 122 rhesus macaques infected with chimeric simian-human immunodeficiency viruses (SHIVs), and showed that B cell priming is the main bottleneck to bNAb elicitation. **Ghosh** and co-authors applied these insights to the design of an immunogen that induces bNAbs with a single vaccination when the right B cell precursor is primed. A single immunization with a germline-targeting trimer generated antibodies that neutralized a wide range of HIV strains in a mouse model with B cells expressing the unmutated common ancestor of a rhesus V2 apex–targeted bNAb.

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