Effect of hospital-admission volume on outcomes following acute non-variceal upper gastrointestinal bleeding

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ABSTRACT

INTRODUCTION: Treatment-requiring acute non-variceal upper gastrointestinal bleeding (NVUGIB) is a common, potentially life-threatening emergency. This study investigated whether hospital admittance volume of patients with NVUGIB was associated with reduced mortality, reduced lasting failure of haemostatic procedures defined as rate of re-endoscopy with repeated haemostasis intervention (ReWHI), transfusion requirements and conversion to surgery.

METHODS: Data on Danish nationwide admissions of patients with acute NVUGIB from 2011-2013 were analysed to estimate 30-day mortality, re-bleeding (ReWHI), transfusion rates and rates of conversion to surgery Data were analysed by regression modelling while controlling for confounders including age, admission haemoglobin, the American College of Anesthesiologists score, comorbidities and the Forrest classification.

RESULTS: A total of 3,537 patients with acute non-variceal upper gastrointestinal bleeding were included in the study. The hospital admission volume of patients with NVUGIB was positively associated with a significant increase in ReWHI with an odds ratio of 1.27; $p = 1.91 \times 10^{-6}$. There was no significant association between admission volume and conversion to surgery, 30-day mortality or transfusion rates.

CONCLUSIONS: A positive association between admission volumes of patients with NVUGIB and ReWHI was identified. No association between admission volumes and 30-day mortality or other failure of haemostasis events could be identified.

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Treatment requiring acute non-variceal upper gastrointestinal bleeding (NVUGIB) is a common emergency with approximately 6,131 annual admissions in Denmark [1]. Advances in the pharmacological and endoscopic treatment in recent decades have reduced re-bleeding and the need for surgery and have therefore reduced mortality [2]. Despite these advances, the 30-day mortality from NVUGIB remains approximately 10-11% [1]. Furthermore, re-endoscopy with repeated haemostasis intervention (ReWHI) within five days has been reported to occur in upwards of 15% of cases [3, 4].

While the 30-day mortality rate is often attributable to terminal malignancy, cardiopulmonary conditions and other comorbidities leading to multiorgan failure rather than actual bleeding [5], other factors besides comorbidity are relevant in explaining the mortality rate. Previous studies have shown that the mortality rates after surgical procedures in, e.g., pancreatic and colorectal cancer are significantly lower when performed in hospitals with higher patient volumes [6].

Whether patients with NVUGIB also benefit from admission to high-volume centres is, however, unknown. This study investigated how the outcome of NVUGIB depends on the volume of patients with NVUGIB at the individual ce ntres in order to evaluate the evidence for centralisation of the treatment of NVUGIB.

We hypothesised that an association exists between hospital admission volumes of patients with NVUGIB and 30-day mortality rates, ReWHI, received units of transfused blood cells and rates of conversion to surgery.

METHODS

This study was approved by the Danish Data Protection Agency. The primary outcome was 30-day mortality. The secondary outcomes were ReWHI, units of transfused red blood cells (RBC) and rates of conversion to surgery.

Data were retrospectively collected from 1 January 2011 to 31 December 2013 from four different Danish national registries.

From the Danish National Patient Registry, we collected information on all admissions where endoscopic haemostatic intervention was performed in the either the duodenum or stomach. The information included hospital admission info, diagnoses and comorbidities as well as conversion to surgery. Comorbidities were defined as International Classification of Diseases, tenth

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version (ICD10) codes indicating a diagnosis of hypertension, diabetes, previous myocardial infarction, atrial fibrillation as well as chronic liver or renal disease

From the Danish Clinical Register of Emergency Surgery (Akut Kirurgi Databasen) [7], data on American Society of Anesthesiologists (ASA) score, admission haemoglobin and haemorrhage stigmata were collected. Transfusion information was extracted from the Danish National Transfusion Database, whereas time of death was collected from the Danish Cause of Death Registry.

Statistical analysis

Statistical analysis was performed using "R" [8]. Hospitals were stratified into quartiles based on their annual volume of NVUGIB admissions. Data were analysed using logistical or linear regression as appropriate. Multiple regression models, associating outcomes with hospital NVUGIB admission volumes, were used and controlled for confounders, including age, sex, admission haemoglobin, ASA score, presence of comorbidities, as defined above, and haemorrhage stigmata defined as a compound grade based on the Forrest classification [9]. Grade 1 equals Forrest grades I-IIb, grade 2 equals IIc and above.

Dichotomous outcomes such as need for ReWHI, conversion to surgery and 30-day mortality are presented as percentages and odds ratios (OR) with 95% confidence intervals (CI), whereas continuous outcomes are reported as medians with interquartile range and as β-coefficients with standard error.

Trial registration: not applicable.

RESULTS

A total of 3,537 patients with treatment-requiring acute NVUGIB were included. Basic demographics are presented in **Table 1**.

The quantitative frequencies of the study endpoints are shown in **Table 2**. Re-bleeding occurred in 20% of cases, resulting in either ReWHI (16.8%) or conversion to surgery (2.9%). RPCs were frequent with a median use of four (2-7) units per patient. Fresh frozen plasma (FFP) and pooled platelets (PLT) were rarely employed with a median use of zero instances and an interquartile use of (0-2) and (0-0), respectively.

TABLE 1

Basic demographics.

Age, yrs, median (IQR)	74 (65-83)
Male gender, %	56.7
Hypertension, %	53.2
Atrial fibrillation, %	25.7
Diabetes, %	17.1
Renal disease, %	11.0
Liver disease, %	6.5
Prior myocardial infarction, %	12.5
ASA score, median (IQR)	3 (2-3)
Admission haemoglobin, mmol/l, median (IQR)	5.1 (4.2-6.1)
Haemorrhage stigmata[a], median (IQR)	1 (1-1)

ASA = American College of Anesthesiologists; IQR = interquartile range.
a) Compound score based on the Forrest classification: grade 1 ≈ grades I-IIb, grade 2 ≈ ≥ IIc.

TABLE 2

Quantitative frequency of the study endpoints (n = 3,537).

Failure of haemostasis and mortality, %	
Need for re-endoscopy	16.8
Conversion to surgery	2.9
30-day mortality	7.2
Transfusion requirements/patient, median (IQR)	
Packed red blood cells, U	4 (2-7)
Fresh frozen plasma, instances	0 (0-2)
Pooled platelets, instances	0 (0-0)

IQR = interquartile range.

TABLE 3

The effect of hospital admission volume of non-variceal upper gastrointestinal bleeding on study endpoints.

	Unadjusted model			Adjusted model		
	OR (95% CI)	β-coefficient (± SE)	p-value	OR (95% CI)	β-coefficient (± SE)	p-value
Need for re-endoscopy	1.06 (1.03-1.09)	-	9.26×10^{-5}	1.28 (1.16-1.42)	-	2.09×10^{-6}
Conversion to surgery	0.75 (0.56-0.98)	-	0.04	0.77 (0.57-1.01)	-	0.06
30-day mortality	1.01 (0.91-1.13)	-	0.81	0.91 (0.78-1.06)	-	0.23
Packed red blood cells transfused	-	-0.14 (± 0.14)	0.32	-	-0.17 (± 0.14)	0.21
Fresh frozen plasma transfused	-	-0.12 (± 0.09)	0.16	-	-0.12 (± 0.08)	0.17
Pooled platelets transfused	-	0.02 (± 0.03)	0.54	-	0.01 (± 0.03)	0.59

CI = confidence interval; OR = odds ratio; SE = standard error.

The effect of NVUGIB hospital admission volume on study end points is presented in **Table 3** and graphically depicted in **Figure 1**. There was no significant association between hospital admission volume and 30-day mortality, conversion to surgery or volume of RBCs transfused (Table 3).

Hospital admission volume stratification was positively associated with a significant increase in ReWHI with an OR of 1.28 (95% CI: 1.16-1.42); $p = 2.09 \times 10^{-6}$.

Subgroup analysis revealed no associations between comorbidities and risk of ReWHI, although atrial fibrillation showed a trend towards and increased risk (OR = 1.28 (95% CI: 1.16-1.42); p = 0.06). In contrast, age (p = 0.04), ASA score (p = 0.04) and Forrest classification (p < 0.01) were all associated with an increased risk of ReWHI.

DISCUSSION

This study found that hospital admission volume of treatment-requiring patients with NVUGIB was positively associated with a significant increase in ReWHI. In contrast, no association with mortality, blood product utilisation or conversion to surgery rates could be identified. These results suggest that ReWHIs were more frequent in hospitals with a high admission volume than in hospitals with a lower admission volume, which runs counter to the initial study hypothesis.

Before drawing conclusions, it is important to underline the difference between initial technical failure of haemostasis related to inadequate haemostasis during the index endoscopy, and late failure, which is often attributed to multiple confounding variables (fluid resuscitation strategies, patient comorbidities, adherence to proton pump inhibitor regimes, etc.). The present study only investigated the association between NVUGIB admission volumes and the above-mentioned predefined outcomes, and the study setup does not allow for a conclusion on whether the observed differences were primarily due to primary haemostasis insufficiency, unnecessary re-endoscopies or late confounding effects. Furthermore, the level of adherence to guidelines mandating dual therapy modalities as well as mandatory proton inhibitor therapy cannot be assessed.

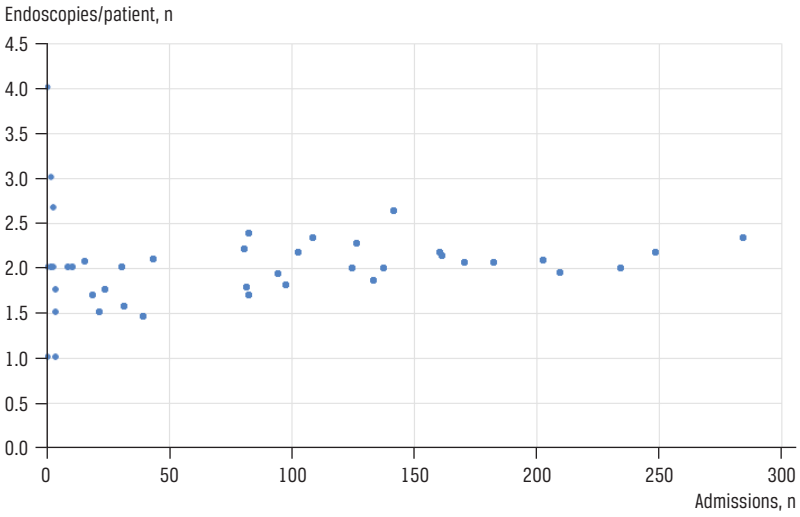
Theoretically, a variety of factors could, however, have had an impact on the observed results. The higher frequency of re-endoscopy with intervention may be driven by the availability of dedicated endoscopy units. In Denmark, hospitals with a high admission volume often have independent endoscopy units or dedicated operating room (OR) facilities to which patients can easily be transferred without having to compete for OR facilities with other patient groups. When faced with a patient exhibiting a continuous slow drop in haemoglobin levels without any signs of frank critical bleeding, the ease of referral to re-endoscopy may result in more rapidly performed re-endoscopies.

This again raises the question of whether a subgroup of subclinical NVUGIP re-bleedings (patients with a gradual drop in haemoglobin levels following their initial endoscopy) may actually be self-limiting, and suggests that a need exists for studies aimed at investigating the optimal criteria for NVUGIP re-endoscopy. Furthermore, it may be speculated that once the decision to perform re-endoscopy was made, the threshold to proceed to actual therapeutic intervention was lower. As such, the easier access to re-endoscopy in high-volume centres may facilitate additional endoscopies, which in turn leads to an increased number of interventions due to the threshold effect. Alternatively, confounding effects such as differences in fluid resuscitation strategies may also be of importance, although a recent study has indicated only a limited association between resuscitation strategy and outcomes following NVUGIB [10].

Another potential aspect may be the fact that high-volume centres often also serve as academic teaching institutions, which may result in an increased ratio of trainee endoscopists, junior attendings or even resident physicians on call. Within the field of colorectal cancer surgery, surgeon volume has been found to improve outcomes with a reduction in 30-day mortality, five-year survival, recurrence, anastomotic leak, hospital stay, operating time and hospital expenses compared with surgeons with a low volume of operations [5].

FIGURE 1

The effect of hospital admission volume of non-variceal upper gastrointestinal bleeding on study end points graphically depicted: the average num ber of endoscopies per patient during admission in relation to the numbers of gastrointestinal haemorrhage admissions to the given hospital requiring treatment during the study period.



It may be speculated that these associations to some degree also apply when treating patients with NVUGIB. While data on the experience level of the endoscopist would have been interesting, unfortunately such data were not available.

It may also be speculated that patients in high-volume hospitals are preselected and more severely ill and therefore more likely to undergo re-endoscopy during admission than patients in hospitals with lower volumes. Including comorbidities and ASA classification in the multivariate model did, however, not underpin this.

These findings contradict previous studies in the field. One study found a significant correlation between hospitals with low admission volume and a negative outcome in high-risk patients with NVUGIB measured on continuous bleeding after treatment, re-bleeding during admission, the need for surgical/other retreatment and death within 30 days following endoscopy [11]. Choi et al pointed out that these findings may be caused by the difference in the number of clips used, and that administration of post-endoscopy proton pump inhibitors was different in the two groups. While we cannot rule out this effect, it is important to note that Danish national guidelines mandate combination therapy, including a minimum of two modalities [12] (e.g., epinephrine injections, cauterisation, clips, etc.) as well as administration of post-endoscopy high-dose proton pump inhibitors. Previous reports have suggested a high degree of adherence to these protocols [3, 4]. Furthermore, these reports do not indicate significant differences in adherence to protocols in high- versus low-volume hospitals.

Although this study does not provide adequate information to assess this, other aspects of haemostasis should be considered when interpreting the results: Novel haemostatic methods are currently under investigation in order to reduce the number of re-bleedings and re-endoscopies in patients with NVUGIB. One study found that the use of haemostatic spray may be appropriate in high-risk patients with a peptic ulcer after adrenaline injection, when other haemostatic measures may not be technically suitable, or as an adjunct to conventional dual therapy in order to achieve primary haemostasis [13]. Other factors like transfusion of PRBC was found to be associated with an increased rate of re-endoscopy as well as conversion to surgery and in-hospital mortality in one study [10]. Furthermore, the timing of surgery has been found to be crucial in lowering in-hospital mortality. Laursen et al found that the optimal timing of endoscopy in haemodynamically stable patients with an ASA-score of 3-5 is 12-36 hours post admission and that haemodynamically unstable patients should undergo endoscopy within three hours following admission [14]. Factors like comorbidity, but not stigmata of the bleeding, have been found to be associated with a decrease in long-term survival [15].

Several studies point out and suggest predictors for re-bleeding after initial endoscopic interventions. One meta-analysis concluded that major predictors of re-bleeding among patients with peptic ulcer bleeding include haemodynamic instability, active bleeding at endoscopy, large ulcer size, ulcer location, haemoglobin value and the need for transfusion [16]. As such, several of the above-mentioned factors could have confounded the observed results.

Regardless of the underlying reason, it is interesting to note that these factors were associated neither with mortality nor with transfusion requirements. As such, even though patients at high-volume centres required more ReWHI, haemostasis (as measured by blood product utilisation) was unaffected. If the initial endoscopic attempt was unsuccessful, one would also have expected higher rates of blood product utilisation. In contrast, blood product utilisation was not associated with hospital admission volumes. These findings might suggest that the ReWHIs performed were, to some extent, unnecessary, which highlights the need for further studies investigating the optimal indications and procedures for re-endoscopy following NVUGIB.

A number of limitations should be acknowledged in this study. As is the case for any retrospective study, the quality of the data relies solely on the quality of the input data. Furthermore, we can only determine associations and not conclude on causal associations.

We adjusted the model for relevant confounders, but we cannot exclude that unidentified confounders may be relevant to this study. Disease severities may not be completely captured by diagnosis codes or ASA classifications. Information regarding anticoagulant use, re-endoscopy without intervention, skill level of the endoscopist as well as timing of endoscopy would have been relevant. Also, access to interventional radiology could be a factor, although referral would theoretically be easier from high-volume centres. Finally, this cohort is representative of patients with upper GI haemorrhage. As such, results may differ if only massive bleeders were analysed.

Further prospective studies are relevant in order to assess the true causation between hospital volume and outcomes of NVUGIB.

CONCLUSIONS

This study found that hospital admission volume was positively associated with a significant increase in the need for re-endoscopy with intervention. This study found no significant association between hospital admission volume and conversion to surgery transfusion blood product administered or 30-day mortality.

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LITERATURE

1. Adamsen S, de Muckadell OB. Behandling af blødende gastroduodenalt peptisk ulcus. Ugeskr Læger 2007;169:1551-5.
2. Wedi E, Fischer A, Hochberger J et al. Multicenter evaluation of first-line endoscopic treatment with the OTSC in acute non-variceal upper gastrointestinal bleeding and comparison with the Rockall cohort: the FLETRock study. Surg Endosc 2018;32:307-14.
3. Danish Clinical Register of Emergency Surgery for Peptic Ulcer. Annual report 2015. Regionernes Kliniske Kvalitetsudviklingsprogram. Aarhus, Denmark, 2016.
4. Danish Clinical Register of Emergency Surgery for Peptic Ulcer. Annual report 2016. Regionernes Kliniske Kvalitetsudviklingsprogram. Aarhus, Denmark, 2017.
5. Sung JJY, Tsoi KKF, Ma TKW et al. Causes of mortality in patients with peptic ulcer bleeding: a prospective cohort study of 10,428 cases. Am J Gastroenterol 2010;105:84-9.
6. Huo YR, Phan K, Morris DL et al. Systematic review and a meta-analysis of hospital and surgeon volume/outcome relationships in colorectal cancer surgery. J Gastrointest Oncol 2017;8:534-46.
7. Møller MH, Larsson HJ, Rosenstock S et al. Quality-of-care initiative in patients treated surgically for perforated peptic ulcer. Br J Surg 2013;100:543-52.
8. A language and environment for statistical computing. Vienna, Austria: Foundation for Statistical Computing, 2013. www.R-project.org/.
9. Forrest JAH, Finlayson NDC, Shearman DJC. Endoscopy in gastrointestinal bleeding. Lancet 1974;304:394-7.
10. Fabricius R, Svenningsen P, Hillingsø J et al. Effect of transfusion strategy in acute non-variceal upper gastrointestinal bleeding: a nationwide study of 5861 hospital admissions in Denmark. World J Surg 2016;40:1129-36.
11. Choi JW, Jeon SW, Kwon JG et al. Volume of hospital is important for the prognosis of high-risk patients with nonvariceal upper gastrointestinal bleeding (NVUGIB). Surg Endosc 2017;31:3339-46.
12. Laursen SB, Jørgensen HS, Schaffalitzky de Muckadell OB. National consensus on management of peptic ulcer bleeding in Denmark 2014. Dan Med J 2014;61(11):C4969.
13. Sinha R, Lockman KA, Church NI et al. The use of hemostatic spray as an adjunct to conventional hemostatic measures in high-risk nonvariceal upper GI bleeding (with video). Gastrointest Endosc 2016;84:900-6.e3.
14. Laursen SB, Leontiadis GI, Stanley AJ et al. Relationship between timing of endoscopy and mortality in patients with peptic ulcer bleeding: a nationwide cohort study. Gastrointest Endosc 2017;85:936-44.e3.
15. Malmi H, Kautiainen H, Virta LJ, et al. Outcomes of patients hospitalized with peptic ulcer disease diagnosed in acute upper endoscopy. Eur J Gastroenterol Hepatol 2017;29:1251-7.
16. García-Iglesias P, Villoria A, Suarez D, et al. Meta-analysis: Predictors of rebleeding after endoscopic treatment for bleeding peptic ulcer. Aliment Pharmacol Ther 2011;34:888-900.