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ORIGINAL ARTICLE

Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS)

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Abstract

Background: A standardized definition of post-hepatectomy haemorrhage (PHH) has not yet been established.

Methods: An international study group of hepatobiliary surgeons from high-volume centres was convened and a definition of PHH was developed together with a grading of severity considering the impact on patients' clinical management.

Results: The definition of PHH varies strongly within the hepatic surgery literature. PHH is defined as a drop in haemoglobin level >3 g/dl post-operatively compared with the post-operative baseline level and/or any post-operative transfusion of packed red blood cells (PRBC) for a falling haemoglobin and/or the need for radiological intervention (such as embolization) and/or re-laparotomy to stop bleeding. Evidence of intra-abdominal bleeding should be obtained by imaging or blood loss via the abdominal drains if present. Transfusion of up to two units of PRBC is considered as being Grade A PHH. Grade B PHH requires transfusion of more than two units of PRBC, whereas the need for invasive re-intervention such as embolization and/ or re-laparotomy defines Grade C PHH.

Conclusion: The proposed definition and grading of severity of PHH enables valid comparisons of results from different studies. It is easily applicable in clinical routine and should be applied in future trials to standardize reporting of complications.

Keywords

liver, resection, hepatectomy, haemorrhage, transfusion, complication

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Introduction

In the 1970s, hepatic resections were still associated with substantial operative mortality (20% for major hepatectomies) with a haemorrhage representing the cause of death in 20% of patients.[1] Several studies have so far demonstrated that a haemorrhage and the need for a transfusion not only adversely affect peri-operative outcome[2,3] but also the long-term prognosis of patients

undergoing a hepatectomy for primary or secondary malignancies.[4–6] Advances in peri-operative management, surgical technique and imaging tools have substantially decreased the risk of intra-operative haemorrhage and the need for a blood transfusion over the past three decades.[7–11] This progress has contributed to the markedly improved outcome of patients undergoing a hepatic resection and high-volumes centres currently report mortality rates below 5%.[2,8,12,13] While elective hepatic resection can nowadays be carried out safely with various transection devices[14] even without routine use of inflow control,[15] post-hepatectomy haemorrhage (PHH) remains an important cause of post-operative morbidity. PHH may require transfusion of packed red blood cells (PRBC), surgical revision and in severe cases might still result in a fatal outcome.

The reported incidence of PHH varies considerably among published studies from 1–8%.[2,12,16,17] Differences in the assessed patient populations as well as surgical and peri-operative management are considered to contribute to the discrepancy in PHH incidence. A major reason for this reported variation may, however, be the lack of a standardized definition and severity grading of this complication resulting in heterogeneous reporting within scientific reports. Moreover, a generally accepted definition of PHH forms the prerequisite for valid comparison of the results from different studies, is thereby helpful to clinicians in evidence-based decision-making and allows for the audit of surgical practice. The importance of uniform definitions of outcome parameters has been highlighted and consensus definitions have been proposed for complications in pancreatic[18–20] and rectal surgery.[21] These definitions have been adopted increasingly by clinicians to report their complications and it can be assumed that they will strongly facilitate comparisons of studies in the future.

Recently, the International Study Group of Liver Surgery (ISGLS) has been convened to develop uniform definitions of major complications after hepatic surgery. Consensus definitions of post-hepatectomy liver failure and bile leakage after hepatic surgery have already been published.[22,23]

In the present study, the consensus definition and grading of severity of PHH is presented with the ultimate goal to standardize reporting of complications in the hepatic surgery literature.

Patients and methods

Literature search

A literature search was performed of the Medline database (Pubmed). Clinical studies on hepatic surgery that were published in the twelve leading surgical journals within the past 5 years were reviewed to evaluate, whether a uniform definition of PHH had already been established among hepatobiliary surgeons and to assess the variability of applied definitions, respectively. The search strategy consisted of combinations of the following search terms: 'liver/hepatic resection', 'hepatectomy', 'complications', 'morbidity', 'mortality, 'haemorrhage' and 'bleeding'. The search was limited to studies on humans that were published in English. While studies on haemorrhage after liver transplantation were excluded, there were no restrictions regarding the indication for a hepatectomy, the underlying status of the liver, or the applied abdominal access (i.e. open or laparoscopic hepatectomy). Reference lists of identified studies were screened manually for additional relevant studies.

Study group

The ISGLS was convened. This group included hepatobiliary surgeons from well-known, high-volume centres with extensive scientific and clinical expertise in the field of hepatic surgery. Drafts of the definition and severity grading of PHH were sent to the ISGLS members for critical review beginning in August 2008. The revised versions of the definition were re-circulated among the members for approval and further comments. At a consensus meeting that was held during the annual meeting of the Australian and New Zealand Hepatic, Pancreatic and Biliary Association Inc (ANZHPBA) at the Sunshine Coast, Queensland, Australia in October, 2008, the proposed definition and grading of PHH was discussed in detail. The members of the study group agreed on using actual patient data (i.e. regular systemic haemoglobin levels after a hepatic resection) for a valid definition of PHH. The first revision of the manuscript considering data on the post-operative course of haemoglobin levels after a hepatic resection in a large set of patients was sent to the members of the study group in November 2009. After the comments of all authors were considered, a second revision was sent to the members of the ISGLS in February 2010. The final version of the manuscript was re-circulated among the authors for approval in March 2010.

Results

Available definitions

The terms 'bleeding' and 'haemorrhage' were most commonly applied to report post-operative blood loss after a hepatic resection. To standardize reporting of this complication and to express its relation to hepatectomy, the term post-hepatectomy haemorrhage (PHH) was suggested.

There is no generally accepted and applied definition of the complication of PHH as indicated by the systematic search of the hepatic surgery literature (Table 1). While the majority of authors did not actually specify this complication, the definitions in the remaining reports varied considerably. In most cases 'clinically significant' PHH was reported as a haemorrhage requiring a minimum amount of PRBCs and surgical revision, respectively. None of the identified studies provided a grading of the severity of PHH. The minimum number of PRBC units that had to be transfused to fulfil the criteria of PHH varied from 1–4 units. In 1994, a proposal for the definition and classification of negative outcomes in solid organ transplantation was published.[38] The authors suggested a system of classifying complications consisting of four grades with subunits. Within this classification post-operative bleeding requiring three or less units of PRBC was staged as grade 1 complication, whereas transfusion of more than three units of PRBC resulted in grade 2a. Subsequently, a classification system of

Table 1 Applied definitions of post-hepatectomy haemorrhage (PHH) in the hepatic surgery literature

Author	Year	*N*	Definition
Virani *et al*.[24]	2007	783	Bleeding requiring >4 units of PRBC
McCormack *et al*.[25]	2007	116	The indications for blood transfusion were massive haemorrhage (>1500 ml) during surgery or a haemoglobin level < 7 g/dl within 24 h after surgery.
Shah *et al*.[26]	2007	193	Post-operative bleeding that required procedures for re-exploration
Abdalla *et al*.[27]	2007	580	Bleeding requiring transfusion and reoperation, respectively
Fujii *et al*.[28]	2007	351	Requiring transfusion of 2 or more units of PRBC, an invasive intervention such as laparotomy or transarterial embolization and monitoring in the surgical intensive care unit within 24 h of the onset of haemorrhage
Petrowsky *et al*.[29]	2006	73	The indications for red blood cell transfusion were a massive haemorrhage (>1500 mL) during surgery or a haemoglobin level < 7 g/dl within 48 h after surgery.
Ogata *et al*.[30]	2006	36	Intra-abdominal haemorrhage requiring reoperation
Cho *et al*.[31]	2006	54	Significant bleeding via drain requiring transfusion
Schroeder *et al*.[17]	2006	587	Excessive postoperative bleeding (>4 units packed red blood cells transfused)
Cho *et al*.[16]	2006	146	Significant bleeding via drain requiring transfusion
Azoulay *et al*.[32]	2006	60	Intra-abdominal haemorrhage requiring re-operation
Miura *et al*.[33]	2006	10	Haemorrhage requiring transfusion of at least 2 units of PRBC within the first 2 h after onset
Ibrahim *et al*.[34]	2006	86	Post-op bleeding includes all forms of haemorrhage, regardless of intervention required
Nagino *et al*.[35]	2005	100	PRBC transfusion with or without FFP transfusion, due to a decrease in haemoglobin concentration to < 7 g/dL or to the development of intra-abdominal bleeding
Kimura *et al*.[36]	2004	64	Post-operative bleeding: requiring surgery or transcatheter arterial embolization
Vauthey *et al*.[37]	2004	127	Haemorrhage from the operative site.
Imamura *et al*.[13]	2003	915	Requiring a red blood cell transfusion for any kind of postoperative bleeding.

PRBC, packed red blood cells; FFP, fresh frozen plasma.

surgical complications in general was published.[39] There is, however, no generally accepted, specific definition of PHH as a major complication after a hepatic resection.

Consensus definition of post-hepatectomy haemorrhage

A thorough analysis of post-operative laboratory values in patients undergoing hepatic resection revealed very little fluctuation of post-operative haemoglobin levels.[40] Considering the regular post-operative course of haemoglobin levels, PHH should be defined as a drop in haemoglobin level >3 g/dl post-operatively compared with post-operative baseline level (i.e. haemoglobin level immediately after surgery) and/or any post-operative transfusion of PRBCs for a falling haemoglobin and/or the need for invasive re-intervention (e.g. embolization or re-laparotomy) to stop bleeding. For the diagnosis of PHH (and to exclude other sources of haemorrhage), evidence of intra-abdominal bleeding should be obtained such as substantial blood loss via the abdominal drains if available (e.g. haemoglobin level in drain fluid >3 g/dl) or detection of an intra-abdominal haematoma or active haemorrhage by abdominal imaging [ultrasound, computed tomography (CT) and angiography]. Patients who are transfused immediately post-operatively for intra-operative blood loss by a maximum of two units of PRBCs are *not* considered to have PHH (i.e. no evidence of active haemorrhage).

Grading

The present definition should be applied to diagnose the complication of PHH. This definition includes all clinical presentations of PHH ranging from asymptomatic haemorrhage to life-threatening conditions. For reporting of PHH, an additional grading system is proposed, which stages PHH into three grades (Grade A, B and C) based on the clinical management required to control the haemorrhage (Table 2).

Post-hepatectomy haemorrhage Grade A

PHH should be classified as grade A, if it can be managed with minimal transfusion requirements (i.e. ≤2 units of PRBCs). The blood loss in these patients results in a limited drop in haemoglobin. These patients can be treated successfully with transient discontinuation of anticoagulation, intravenous fluid therapy and transfusion of PRBCs. Transfusion of PRBC should, however, not only depend on actual blood loss but also on the patient's age and comorbidities, in particular, the presence of coronary artery disease. In general, patients with PHH grade A do not develop clinical symptoms and can usually be managed on a regular ward. The hospital stay of these patients is usually not prolonged.

Post-hepatectomy haemorrhage Grade B

Grade B PHH should be defined as a haemorrhage that requires transfusion of more than two units of PRBCs. In addition to

Table 2 Consensus proposal of the ISGLS for the definition and severity grading of post-hepatectomy haemorrhage (PHH)

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. 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

discontinuing anticoagulants, coagulation products (fresh frozen plasma, FFP; coagulation factors; platelets) may be administered. Their management, however, does not require invasive intervention. Patients who undergo angiography with no interventional treatment (i.e. no embolization) are also diagnosed with PHH Grade B. The drop in haemoglobin level (compared with the initial post-operative value) in patients with Grade B PHH exceeds 3 mg/dl (unless transfusion is started early). These patients may develop symptoms of hypovolemia such as hypotension and tachycardia. There is commonly detectable free intra-abdominal fluid/haematoma on abdominal imaging and blood loss via the abdominal drains (if present), respectively. Patients with a grade B PHH are commonly treated and monitored on an intermediate or intensive care unit. The patient's hospital stay may be prolonged.

Post-hepatectomy haemorrhage Grade C

Patients developing PHH grade C are in a life-threatening condition requiring radiological interventional treatment (such as embolization) or re-laparotomy to control the bleeding. The clinical presentation of these patients includes blood loss via intra-abdominal drains (if present) in combination with a drop in the haemoglobin level > 3 mg/dl (compared with the first post-operative value). However, owing to blood clots obstructing the drains, patients with PHH Grade B/C may also present with abdominal pain or distension and low drain output. Patients with PHH Grade C may be haemodynamically unstable requiring treatment with vasopressors in addition to fluid therapy. In severe cases, development of (multi-) organ failure and hypovolemic shock may occur. These patients are transferred to an intensive care unit. The hospital stay of these patients is prolonged.

Table 3 summarizes the clinical characteristics of patients diagnosed with different grades of PHH.

Validation of the definition and grading of post-hepatectomy haemorrhage

The present definition and grading of severity of PHH was applied to patients who underwent liver resection at the Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Germany. A total of 835 patients who were operated between January 2002 and January 2008 were included in this analysis. Twenty-eight (3%) patients were diagnosed with the complication of PHH. Of these, four (14%) patients fulfilled the proposed criteria of PHH Grade A. PHH Grade B was diagnosed in 12 (43%) patients who underwent a change in their clinical management. Finally, 12 (43%) patients underwent invasive re-intervention owing to PHH and were therefore classified as having Grade C PHH.[40] In the analysis of all patients who underwent a hepatic resection transfusion of up to two units of PRBCs was associated with an in-hospital mortality rate of 1.4% (10 of 733 patients), whereas it was 25.2% (26 of 102 patients) for patients who received more than two units of RPBCs was ($P < 0.0001$; Fisher's exact test). The in-hospital mortality associated with PHH Grade A, B and C was 0%, 17% ($n = 2$) and 50% ($n = 6$), respectively.

Discussion

There is increasing awareness of the importance and value of generating uniform definitions of outcome parameters to enable reliable comparison of the results from different studies and ultimately to provide patients with the best available therapy. Although the mortality of patients undergoing a hepatic resection has been reduced substantially within the past two decades, morbidity rates remain high and still account for 30–45%.[2,8,13,17] The reasons for the persistently high morbidity remain subject to discussion and may, in part, be explained by changes in the population of patients undergoing hepatic surgery such as a higher proportion of patients with advanced disease, significant comorbidities and/or previous chemotherapy. Standardized definitions of major complications are required to evaluate advances in surgical technique and peri-operative care that might potentially reduce peri-operative morbidity. The most relevant procedure-specific complications after a hepatic resection are post-hepatectomy liver failure, bile leakage and PHH. Consensus definitions for the diagnosis and severity grading of post-hepatectomy liver failure and bile leakage after hepatic resection have recently been published.[22,23] While a standardized definition and severity grading of post-pancreatectomy haemorrhage has already been suggested,[20] a uniform definition of PHH has been

Table 3 Common clinical characteristics of patients with different severity grades of post-hepatectomy hemorrhage (PHH)

	Grade A	Grade B[a]	Grade C
Clinical condition[b]	Not impaired	Impaired	Life-threatening
Clinical symptoms	No	May have hypotension and tachycardia	May have haemodynamic instability (severe hypotension and tachycardia) Potential hypovolemic shock with organ dysfunction/failure
Adequate response to transfusion of PRBCs[c]	Yes	Yes/no	No
Need for diagnostic assessment	No	Yes	Yes
Radiological evaluation	Possible free intra-abdominal fluid/ haematoma	Free intra-abdominal fluid/ hematoma May have active bleeding on angiography	Free intra-abdominal fluid/ haematoma Active bleeding on angiography
Hospital stay	Commonly not prolonged	Commonly prolonged	Prolonged
Specific treatment	Discontinuation of anticoagulants Intravenous fluid therapy Transfusion of ≤2 units of PRBCs	Discontinuation of anticoagulants Intravenous fluid therapy Transfusion of >2 units of PRBCs	Discontinuation of anticoagulants Intravenous fluid therapy Transfusion of PRBCs Vasopressor therapy Embolization and/ or re-laparotomy

[a]Patients who undergo angiography with no interventional treatment (i.e. no embolization) are diagnosed with PHH Grade B. Moreover, patients developing infected intra-abdominal haematoma requiring percutaneous drainage are classified to have PHH Grade B but are not listed in this table because of their different and infrequent presentation.
[b]Impaired clinical condition is defined as a clinical condition that is worse compared with patients without a complication but does not require additional organ support other than oxygen (via nasal canula/mask) and diuretics. Life-threatening clinical condition is defined as clinical condition requiring additional organ support (e.g. vasopressor therapy, mechanical ventilation and haemodialysis).
[c]An adequate response to transfusion of one unit of PRBC is defined as a rise of the haemoglobin level of ≥0.7 g/dl.
PRBC, packed red blood cells.

lacking as confirmed by our systematic literature search. There is a wide range of descriptions of the complication of PHH within published studies, whereas in the majority of articles no definition of PHH was mentioned.

The present consensus definition of PHH represents the first attempt to standardize the diagnosis of this complication for academic as well as routine clinical application. We suggest defining PHH as a drop in haemoglobin level >3 g/dl post-operatively compared with the post-operative baseline haemoglobin level. Furthermore, PHH should be diagnosed in cases requiring a post-operative transfusion of PRBCs for a falling haemoglobin and/or the need for radiological intervention (such as embolization) and/or re-laparotomy to stop bleeding. The diagnosis of PHH requires evidence of intra-abdominal bleeding, that may be present either as blood loss via the abdominal drains or detection of an intra-abdominal haematoma or an active haemorrhage by abdominal imaging (ultrasound, CT and angiography). Other sources of haemorrhage should be ruled out. Patients who do not have evidence of an active haemorrhage (e.g. falling haemoglobin, blood loss via abdominal drain or on imaging) and who receive a transfusion immediately post-operatively as a result of intra-operative blood loss by a maximum of two units of PRBCs are *not* considered to have PHH.

The post-operative drop in haemoglobin to define PHH is controversial. The present proposal to define PHH as a drop in haemoglobin >3 g/dl was based on an extensive analysis of the regular post-operative course of systemic haemoglobin after hepatic resection.[40] As the present study included patients who received no blood transfusion post-operatively and had an uneventful post-operative course, it demonstrated the natural kinetics of post-operative haemoglobin levels. As already shown in a smaller previous study,[41] this analysis revealed only very little fluctuation of systemic haemoglobin levels during the post-operative course including the initial post-operative period. Thus a drop of 3 g/dl displays a significant haemorrhage that is usually not confounded by haemodilution and measurement inaccuracies (in particular for blood gas analyses). It should, however, be noted that when a haemorrhage is noticed early (e.g. by blood loss via abdominal drains) and a transfusion is started shortly thereafter, the drop in haemoglobin might not reach 3 g/dl. To consider this scenario, patients receiving a post-operative transfusion for a falling haemoglobin are also diagnosed with PHH.

The severity of PHH may vary from asymptomatic bleeding to life-threatening conditions. While most of the identified definitions applied in published studies included a clinical criterion to diagnose PHH, none of these provided a classification system of the severity of PHH. To describe more precisely the severity of PHH, we propose a grading system incorporating the impact of this complication on patients' clinical management. On the basis of the proposed definition of PHH, asymptomatic patients who

can be managed with a minimal amount of blood transfusion (i.e. ≤2 units of PRBCs) are categorized as having Grade A PHH, whereas those patients requiring >2 units of PRBCs and may be managed without invasive therapy are diagnosed with Grade B PHH. Finally, those patients who require radiological intervention or re-laparotomy owing to PHH fulfil the criteria for Grade C. As opposed to the definition of post-pancreatectomy haemorrhage the present definition and grading of severity of PHH does not include the time of onset and the location of bleeding. Although it is accepted that the time of onset (e.g. early vs. late) and location of bleeding (e.g. cut surface vs. hilar vasculature) may be used to describe and characterize PHH, we deliberately did not incorporate these variables into our proposal in an attempt to develop a rather simple definition. The proposed grading system reflects the severity of the haemorrhage as indicated by the amount of blood transfusion and need for invasive therapy. This approach, moreover, implies potential adverse effects of the required therapy. A blood transfusion has been demonstrated as a risk factor for perioperative morbidity[3] and for poor long-term survival in patients with malignancy.[42,43] Invasive therapy exposes patients to the risks of further complications. Moreover, the approach to grade the severity of PHH based on the clinical sequelae is in line with the grading of other complications[18–21] as well as a general classification of operative complications.[38,39] From a clinical point of view we are therefore convinced that the impact of a haemorrhage on a patient's management is of primary relevance to the patient and the surgeon and should be used to grade the severity of PHH. In our view the proposed definition and grading of severity of PHH should not be used in lieu of available general classifications of surgical complications but in addition to these to enable a more accurate description of the adverse events occurred.

The present proposal for the definition and severity grading of PHH is simple to use and easily applicable to patients undergoing a hepatic resection. Furthermore, the reporting of PHH according to the present proposal is reproducible and thus suitable for application within prospective and retrospective clinical studies. It was a primary objective of the members of the study group to agree upon a definition using parameters that are applied routinely in clinical practice. It was a further intention to limit the use of laboratory values and quantitative parameters for the diagnosis and severity grading of PHH as far as possible. For this and practical reasons, the haemoglobin level in the drain fluid was not incorporated as a mandatory component of the diagnosis of PHH. We are well aware that the proposed thresholds of the amount of transfused PRBCs are only a suggestion and the consequences on clinical management are subject to the executing physician's decision-making on the individual patient. In particular, there remains debate on the optimal management of patients who develop a delayed massive haemorrhage. Angiography with the intention of performing embolization might offer a minimally invasive treatment option to avoid further surgery. However, an analysis of 1010 patients who underwent pancreatic and biliary surgery at a single institution revealed that only a minority of patients were treated with embolization and the authors reported aggressive surgical intervention as the reference therapy for patients with delayed massive haemorrhage.[44] A recent study on 351 patients who underwent surgery for malignant pancreatobiliary disease suggested transarterial embolization as a useful treatment option, if performed distal to the common hepatic artery or actually to the common hepatic artery when there is sufficient collateral hepatic blood flow.[28] As a further strategy patients may undergo angiography with prophylactic placement of a stent before re-laparotomy to treat the underlying cause of haemorrhage (e.g. bile leakage) and evacuation of intra-abdominal haematoma, respectively. As in the current proposal, radiological intervention or re-laparaotomy define patients with Grade C PHH, this discussion does not affect the applicability of our proposed grading system.

The present standardized definition should substantially unify reporting of PHH in the hepatic surgery literature while enabling comparison and pooling of the results from different studies. It is recommended to use the proposed classification and grading system in all future studies dealing with hepatic resections. However, further studies providing prospective validation of the proposed definition and grading of severity of PHH are required to achieve higher levels of validation.

Conflicts of interest

None declared.

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