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# Incidence and risk factors for life-threatening bleeding after allogeneic stem cell transplant

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## Summary

Bleeding is a frequent complication after allogeneic haematopoietic stem cell transplantation (HSCT) and may affect survival. The purpose of this study was to determine the incidence and risk factors for life-threatening bleeding after HSCT by retrospective evaluation of 491 allogeneic HSCT recipients. With a median follow-up of 33 months, 126 out of 491 allogeneic HSCT recipients experienced a haemorrhagic event (25·7%) and 46 patients developed a life-threatening bleeding episode (9·4%). Pulmonary and gastrointestinal bleeding were the most common sites for life-threatening bleeding, followed by central nervous system. In multivariate analyses, the presence of severe thrombocytopenia after day +28 and the development of grade III–IV acute graft-*versus*-host disease (GVHD) or thrombotic microangiopathy (TMA) retained their association with life-threatening bleeding events. The overall survival at 3 years among patients without bleeding was 67·1% for only 17·1% for patients with life-threatening bleeding ($P < 0·001$). In conclusion, life-threatening bleeding is a common complication after allogeneic HSCT. Prolonged severe thrombocytopenia, acute grade III–IV GVHD and TMA were associated with its development.

**Keywords:** graft-*versus*-host disease, haematopoietic stem cell transplantation, haemorrhage, risk factors, thrombocytopenia.

Allogeneic haematopoietic stem cell transplantation (HSCT) is the curative therapy for many haematological disorders and its use has increased markedly over the past two decades. Graft-*versus*-host disease (GVHD), infection and recurrent malignancy are the most common complications of allogeneic HSCT. However, recent studies have recognized that one-third of allogeneic HSCT recipients suffer at least one bleeding episode (Nevo *et al*, 1998, 1999; Pihusch *et al*, 2002; Bacigalupo, 2003; Labrador *et al*, 2013).

Prolonged severe thrombocytopenia and tissue damage, caused by conditioning regimen or post-transplant complications, leads to a more pronounced bleeding tendency among allogeneic HSCT recipients (Nevo *et al*, 1999; Pihusch *et al*, 2002; Bacigalupo, 2003; Pihusch, 2004; Gerber *et al*, 2008; Holler *et al*, 2009; Labrador *et al*, 2013). Moreover, haemorrhagic complications may have an adverse effect on overall survival in these patients (Nevo *et al*, 1998, 1999, 2007; Bacigalupo, 2003; Holler *et al*, 2009; Labrador *et al*, 2013). Identification of patients at risk of life-threatening bleeding (i.e. where the patient is at immediate risk of dying) and successful management of bleeding following stem cell transplants is essential in order to achieve and maintain a favourable outcome. Although several risk factors for developing any bleeding episodes in this setting have been identified, clinical variables for developing life-threatening bleeding after allogeneic HSCT have not yet been identified.

The purpose of this study was to determine the incidence and risk factors for life-threatening bleeding after allogeneic HSCT.



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## Subjects and methods

### *Subjects*

Analyses were performed in accordance with the Declaration of Helsinki and the guidelines of the institutional review board of the Hospital Universitario de Salamanca. This study was approved by the Salamanca University Hospital Ethics Committee. We conducted a retrospective cohort study of all consecutive patients (aged >18 years) who had undergone allogeneic HSCT between 1995 and 2012 at the Hospital Universitario de Salamanca. The conditioning regimen provided was appropriate to the primary disease and type of transplant and could be divided into a myeloablative regimen and reduced-intensity conditioning (RIC). Prophylactic platelet transfusion was given when the platelet count fell below $10 \times 10^9$/l or 10–$20 \times 10^9$/l in those with fever (>38°C). In the absence of complications, patients were discharged from the hospital once stem cell engraftment had been achieved. All bleeding events after allogeneic HSCT were recorded; only documentation of isolated mild petechiae was excluded from our analysis. Other post-HSCT complications, such as infections, GVHD, veno-occlusive disease (VOD) and thrombotic microangiopathy (TMA), were also recorded. GVHD was defined by clinicopathological criteria for the diagnosis and staging of the condition (Shulman *et al*, 1980; Przepiorka *et al*, 1995; Filipovich *et al*, 2005). VOD was diagnosed according to the Modified Seattle Criteria (Jones *et al*, 1987). A diagnosis of TMA was made in patients with microangiopathic haemolytic anaemia, thrombocytopenia and high levels of serum lactate dehydrogenase (Labrador *et al*, 2014).

### *Outcomes*

The primary end-points of the study were the incidence, risk factors and clinical impact of post-allogeneic HSCT life-threatening haemorrhages. The location and number of bleeding sites were recorded. Bleeding was considered a major event if it caused a reduction in the haemoglobin level of at least 20 g/l, transfusion of at least two of blood, or symptomatic bleeding in a critical area or organ. Transfusion events due to aplasia post-chemotherapy were not included. Major bleeding was considered to be life-threatening if it resulted in death, symptomatic intracranial or pulmonary bleeding, bleeding with a decrease in the haemoglobin level of at least 50 g/l, or bleeding requiring transfusion of at least 4 units of blood, inotropic agents or necessitating surgery. All other bleeding was considered to be minor. Mild petechiae were not included in the analysis.

### *Statistics*

A descriptive statistical analysis was performed after compiling the data in an Excel (Microsoft) spreadsheet. Results were expressed as percentages for categorical variables and as medians (and standard deviations) for continuous variables. Differences between groups were evaluated by Student's *t*-test and Mann–Whitney *U*-test for normally and non-normally continuous variables, respectively, and the chi-squared-test for categorical variables, using IBM SPSS Statistics 19.0 (SPSS, Chicago, IL, USA). The incidence of life-threatening bleeding and the overall survival were calculated using the Kaplan–Meier method. The two-sided log-rank test was used to identify risk factors for developing life-threatening bleeding and to compare survival curves. All the parameters that were significant in univariate analyses, age and gender were included in a multivariate analysis using Cox proportional hazard models. Statistical significance of all tests was accepted for values of $P < 0{\cdot}05$.

## Results

### *Baseline characteristics of patients*

The main demographic and haematological features of the 491 evaluable allogeneic HSCT recipients are shown in Table I. The mean age was $46 \pm 13$ years, and 61% of patients were male ($n = 300$). 353 patients (72%) received an allogeneic HSCT from a related donor. Most patients (81·7%) received a peripheral blood stem cell transplant and 279 patients (56·8%) received RIC. The main complications following HSCT are shown in Table I.

### *Incidence of fatal bleeding after allogeneic HSCT*

With a median follow-up of 33 months (range, 1–171 months), 126 out of 491 allogeneic HSCT recipients experienced a haemorrhagic event (25·7%), and 46 patients experienced a life-threatening bleeding episode (9·4%), representing 36·5% of all bleeding patients. The cumulative incidence of life-threatening bleeding in allogeneic HSCT recipients was 14·6% at 10 years (Fig 1), although most of them ($n = 42$) occurred within 2 years post-HSCT. Pulmonary bleeding was the most common site for life-threatening bleeding in allogeneic HSCT recipients ($n = 16$, 34·8%) (Table II), followed by the gastrointestinal tract ($n = 14$, 30·4%), central nervous system ($n = 12$, 26·1%) and other locations ($n = 4$, 8·7%).

### *Risk factors for life-threatening bleeding development after allogeneic HSCT*

Table III shows the results of the univariate and multivariate analyses carried out to identify the variables capable of predicting life-threatening bleeding episodes after allogeneic HSCT. Advanced stage, allo-HSCT from unrelated donor, GVHD prophylaxis other than calcineurin inhibitors (ciclosporin or tacrolimus) plus methotrexate, use of antithymocyte globulin, umbilical cord transplantation, severe thrombocytopenia (platelet count $<20 \times 10^9$/l) after day +28, grade III–IV acute GVHD and TMA were significantly

**Table I.** Baseline characteristics of patients and main complications after HSCT ($n$ = 491).

| Variable | Total | Life-threatening bleeding ($n$ = 46) | Non-life-threatening bleeding ($n$ = 445) | $P$ |
|---|---|---|---|---|
| Age, years (median ± SD) | 46·10 ± 13·02 | 44·33 ± 12·94 | 46·29 ± 13·03 | 0·331 |
| Sex (male/female) (%) | 300 (61·1)/191 (38·9) | 26 (56·5)/20 (43·5) | 274 (61·6)/171 (38·4) | 0·503 |
| Donor | | | | |
| Related allogeneic | 353 (71·9) | 26 (56·5) | 327 (73·5) | 0·015 |
| Unrelated allogeneic | 138 (28·1) | 20 (43·5) | 118 (26·5) | |
| Stage of disease | | | | |
| Low risk | 230 (46·8) | 22 (47·8) | 208 (46·7) | 0·083 |
| Intermediate risk | 154 (31·4) | 9 (19·5) | 145 (32·6) | |
| Advanced risk | 107 (21·8) | 15 (32·6) | 92 (20·7) | |
| Source of stem cells | | | | |
| Peripheral blood | 401 (81·7) | 32 (69·6) | 369 (82·9) | 0·016 |
| Bone marrow | 71 (14·5) | 9 (19·6) | 62 (13·9) | |
| Umbilical cord | 19 (3·9) | 5 (10·9) | 14 (3·1) | |
| Conditioning regimen | | | | |
| RIC | 279 (56·8) | 22 (47·8) | 257 (57·8) | 0·196 |
| Myeloablative | 212 (43·2) | 24 (52·2) | 188 (42·2) | |
| GVHD prophylaxis | | | | |
| CNI (TAC or CsA) + MTX | 353 (71·9) | 30 (65·2) | 323 (72·6) | 0·001 |
| CNI (TAC or CsA) + MMF | 33 (6·7) | 9 (19·6) | 24 (5·4) | |
| TAC/SIR | 77 (15·7) | 3 (6·5) | 74 (16·6) | |
| Others | 28 (5·7) | 4 (8·7) | 24 (5·4) | |
| Complications after HSCT | | | | |
| Grade 0–II acute GVHD | 425 (86·6) | 30 (65·2) | 395 (88·8) | |
| Grade III–IV acute GVHD | 66 (13·4) | 16 (34·8) | 50 (11·2) | <0·001* |
| Extensive chronic GVHD | 135 (27·5) | 10 (21·7) | 125 (28·1) | 0·358† |
| Veno-occlusive disease | 27 (5·5) | 5 (10·9) | 22 (4·9) | 0·093‡ |
| Thrombotic microangiopathy | 41 (8·4) | 12 (26·1) | 29 (6·5) | <0·001§ |

RIC, reduced-intensity conditioning; GVHD, graft-*versus*-host disease; CNI, calcineurin inhibitors; TAC, tacrolimus; CsA, ciclosporin; MTX, methotrexate; MMF, mycophenolate mofetil; SIR, sirolimus; HSCT, haematopoietic stem cell transplantation; SD, standard deviation.
Stage of disease: low risk (first complete remission or chronic phase), high risk (relapse or progressive disease, blast crisis) and intermediate risk (all others).
*Compared with grade 0–II acute GVHD.
†Compared with those without extensive chronic GVHD.
‡Compared with those without veno-occlusive disease.
§Compared with those without thrombotic microangiopathy.

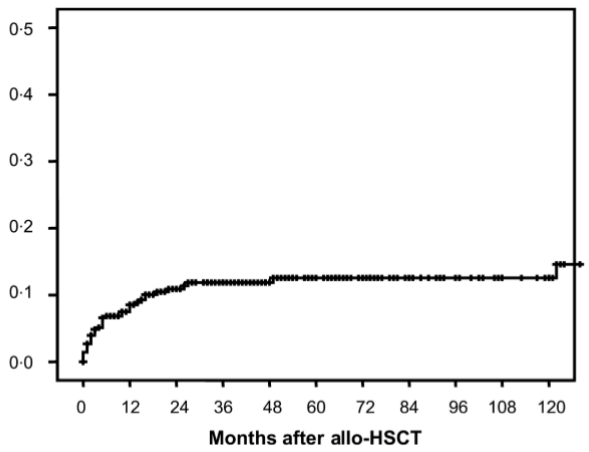


**Fig 1.** Cumulative incidence of life-threatening bleeding. Allo-HSCT, allogeneic haematopoietic stem cell transplant.

associated with life-threatening bleeding complications in the univariate analysis. In multivariate analyses, only the presence of severe thrombocytopenia after day +28 [Hazard ratio (HR) = 3·20, 95% confidence interval (CI) = 1·53–6·68, $P$ = 0·002] and the development of grade III–IV acute GVHD (HR = 2·60, 95% CI = 1·26–5·35, $P$ = 0·009) and TMA (HR = 2·45, 95% CI = 1·12–5·33, $P$ = 0·024) retained their association with life-threatening bleeding events.

### *Outcome of life-threatening bleeding development after allogeneic HSCT*

Bleeding was the cause of death in 29 out of 46 patients with life-threatening bleeding (63%).

Severity of bleeding had a significant influence on outcome (Fig 2). The overall survival at 3 years among patients

**Table II.** Bleeding episodes after haematopoietic stem cell transplantation.

| Location | All episodes (%) | Life-threatening (%) | Non-life-threatening (major/minor) (%) |
|---|---|---|---|
| Mucosal | 12 (9·5) | 0 | 12 (15·0) |
| Genitourinary | 30 (23·8) | 0 | 30 (37·5) |
| Gastrointestinal | 44 (34·9) | 14 (30·4) | 30 (37·5) |
| Pulmonary | 16 (12·7) | 16 (34·8) | 0 |
| Central nervous system | 12 (9·5) | 12 (26·1) | 0 |
| Gynaecological | 3 (2·4) | 0 | 3 (3·7) |
| Others | 9 (7·1) | 4 (8·7) | 5 (6·3) |
| Total | 126 (100) | 46 (100) | 80 (100) |

without bleeding was 67·1%, but only 17·1% for patients with life-threatening bleeding ($P < 0·001$).

Moreover, acute grade III–IV GVHD was associated with a worse outcome among patients with life-threatening bleeding (Fig 3A); median overall survival was 7 months for life-threatening bleeding patients without severe acute GVHD compared with 3 months for those with severe acute GVHD ($P = 0·010$). Figure 3B illustrates the overall survival among patients without life-threatening bleeding with or without acute grade III–IV GVHD.

## Discussion

Bleeding is a frequent complication after allogeneic-HSCT and is associated with poor survival after in these cases. Consistent with other series, 25% of patients experienced at least one bleeding episode (Nevo *et al*, 1998, 1999; Pihusch *et al*, 2002; Bacigalupo, 2003). Although several reports found gastrointestinal and genitourinary locations to be the most common sites for bleeding after allogeneic-HSCT, death from bleeding is rarely reported (<10% of deaths after allo-HSCT) except when due to diffuse alveolar haemorrhage and intracranial haemorrhage. In our series, one-third of bleeding patients suffered life-threatening bleeding, which represents a cumulative incidence of 11% at 10 years in all allogeneic HSCT recipients, and 63% of them died from their bleeding.

Pulmonary and gastrointestinal bleeding were the most common sites for life-threatening bleeding in allogeneic HSCT recipients (corresponding to two-thirds of all life-threatening bleeding episodes), followed by central nervous system (26·1%). Given that adverse effects of bleeding on survival were correlated with bleeding intensity it is essential to study the life-threatening risk factors if the overall survival of these patients needs to be improved. However, little is known about bleeding complications, and most other studies have analysed bleeding episodes without considering their severity, or have focused on a single bleeding location. To our knowledge, this is the first study to attempt to determine risk factors for life-threatening bleeding complications after allogeneic-HSCT.

The risk factors for life-threatening bleeding in our series were prolonged severe thrombocytopenia, severe acute GVHD and TMA, but not other variables that have been found to be associated with bleeding episodes in other studies, such as a myeloablative conditioning regimen, use of antithymocyte globulin, umbilical cord transplantation, VOD and the administration of anticoagulant therapy (Labrador *et al*, 2013).

Prolonged severe thrombocytopenia has previously been associated with bleeding complications (Pihusch *et al*, 2002; Labrador *et al*, 2013), and has been reported as a risk factor for intracranial haemorrhage in several studies (Pomeranz

**Table III.** Univariate and multivariate analyses of factors influencing life-threatening bleeding episodes.

| Variable | Univariate *P* | Multivariate *P* | Hazard ratio (95% CI) |
|---|---|---|---|
| Ag > 45 years | 0·494 | 0·286 | 1·42 (0·74–2·71) |
| Male sex | 0·694 | 0·743 | 1·11 (0·60–2·04) |
| Advanced disease | 0·004 | 0·100 | 1·74 (0·90–3·37) |
| Unrelated donor | 0·002 | 0·844 | 1·08 (0·50–2·33) |
| Ablative conditioning regimen | 0·351 | – | – |
| GVHD prophylaxis (CNI + MTX vs. others) | 0·007 | 0·372 | 0·71 (0·33–1·51) |
| Use of ATG | <0·001 | 0·128 | 2·17 (0·80–5·89) |
| Umbilical cord transplantation* | 0·002 | 0·749 | 1·23 (0·34–4·41) |
| Severe thrombocytopenia after day 28 | <0·001 | 0·002 | 3·20 (1·53–6·68) |
| Anticoagulation after HSCT | 0·372 | – | – |
| Grade III–IV acute GVHD† | <0·001 | 0·009 | 2·60 (1·26–5·35) |
| Extensive chronic GVHD‡ | 0·073 | – | – |
| Veno-occlusive disease | 0·080 | – | – |
| Thrombotic microangiopathy | <0·001 | 0·024 | 2·45 (1·12–5·33) |

GVHD, graft-*versus*-host disease; CNI, calcineurin inhibitors; MTX, methotrexate; ATG, antithymocyte globulin.

*Compared with bone marrow or peripheral blood stem cells.

†Compared with non-acute GVHD plus grade I–II acute GVHD.

‡Compared with limited or non-chronic GVHD.

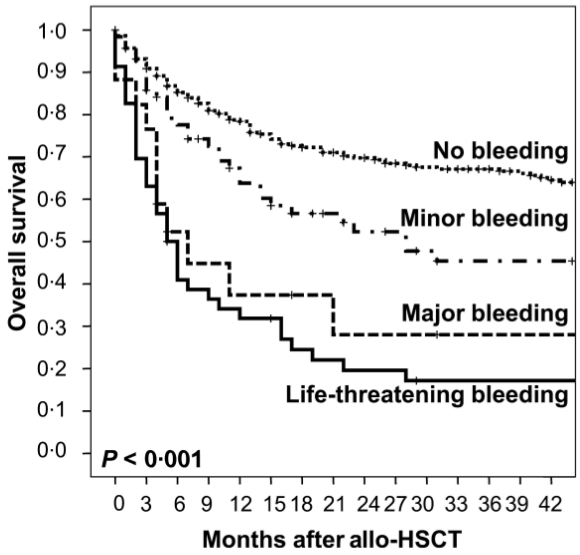


**Fig 2.** Overall survival according to severity of bleeding. Allo-HSCT, allogeneic haematopoietic stem cell transplant.

*et al*, 1994; Graus *et al*, 1996; Colosimo *et al*, 2000; Nevo & Vogelsang, 2001). Here, we have also identified thrombocytopenia as a main cause of bleeding from other sites, such as pulmonary haemorrhage and gastrointestinal or genitourinary bleeding. Previous studies have also shown that when prophylactic platelet transfusion was given, profound thrombocytopenia was not the only key risk factor in most bleeding events following HSCT (Nevo & Vogelsang, 2001; Nevo *et al*, 2007). Additionally, the thrombocytopenia becomes more severe and prolonged in patients who develop GVHD (Bacigalupo, 2003). Therefore, the role of other factors in pathophysiology of life-threatening bleeding must be emphasized.

Development of acute GVHD has also been associated with bleeding complications (Nevo *et al*, 1999; Pihusch *et al*, 2002; Bacigalupo, 2003; Gerber *et al*, 2008) and its severity is closely correlated with the severity of bleeding episodes (Nevo *et al*, 1999; Bacigalupo, 2003). Our results are in accordance with this, and we have clarified that acute grade III–IV GVHD, but not chronic GVHD, is associated with life-threatening bleeding. Previously, grade III–IV acute GVHD have been associated with intracranial haemorrhage (Najima *et al*, 2009), pulmonary haemorrhage and gastrointestinal bleeding (Nevo *et al*, 1999), which accounted for more than 90% of the life-threatening bleeding episodes in our series. Cumulative endothelial and epithelial damage through immunological injury to the vasculature could explain the risk of bleeding in GVHD (Dumler *et al*, 1989). Another possible mechanism is the reduction of factor XIII (FXIII) levels in patients with GVHD of the gut, whose FXIII levels are known to be below the normal range, and a correlation between FXIII activity and severity of GVHD.

Patients who developed TMA had a higher risk of life-threatening bleeding. It is of particular note that TMA development was also associated with severe acute GVHD in several studies (Shimoni *et al*, 2004; Nakamae *et al*, 2006; Batts & Lazarus, 2007; Worel *et al*, 2007; Changsirikulchai *et al*, 2009; Willems *et al*, 2010; Labrador *et al*, 2014). Therefore, given that aggressive treatment against underlying mechanisms of life-threatening bleeding may improve survival after allo-HSCT, the improvement of acute GVHD treatment would be crucial, because it leads to a poorer outcome in these patients.

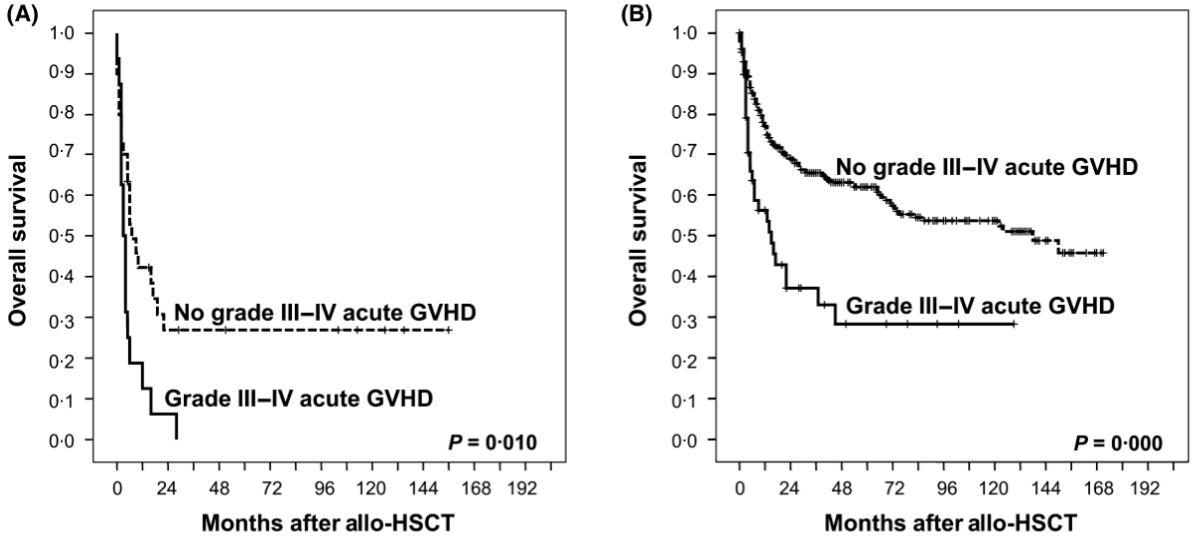


**Fig 3.** (A) Overall survival among patients with life-threatening bleeding with or without acute grade III–IV GVHD. (B) Overall survival among patients without life-threatening bleeding with or without acute grade III–IV GVHD. Allo-HSCT, allogeneic haematopoietic stem cell transplant; GVHD, graft-*versus*-host disease.

In conclusion, life-threatening bleeding is a common complication after allogeneic HSCT. Prolonged severe thrombocytopenia, acute grade III–IV GVHD and TMA were identified as the main risk factors for its development. However, a large multicentre register could be needed to identify and validate the individual risk for life-threatening bleeding.

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## Authorship

JRG-P and JL conceived the study; MS-B and JL performed the statistical analysis; JL and JRG-P wrote the paper; JL collected the data and critically reviewed the paper; DC, LL-C, LV, FS-G, CG, IA, MCC and JRG-P provided the patients and critically reviewed the paper; all authors approved the final version of the paper.

## Competing interests

All authors declare no competing financial interests in relation to the work described.

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