Blood Reviews 60 (2023) 101076

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Definitions, incidence and outcome of poor graft function after hematopoietic cell transplantation: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Poor graft function
Hematopoietic cell transplantation
Bone marrow transplantation
Systematic review, outcome

ABSTRACT

Poor graft function (PGF) after allogeneic hematopoietic stem cell transplantation (HCT) is a serious complication with high morbidity and mortality. The reported incidence of PGF, its risk factors and outcome vary substantially between studies. This variability may be explained by heterogeneity in patient cohorts and HCT strategies, differences in the underlying causes of cytopenia, as well as by differences in PGF definition. In this systematic review and meta-analysis, we provide an overview of the various PGF definitions used and determined the impact of this variability on the reported incidence and outcome. We searched MEDLINE, EMBASE and Web of Science up to July 2022, for any study on PGF in HCT recipients. We performed random-effect meta-analyses for incidence and outcome and subgroup analyses based on different PGF criteria. Among 69 included studies (14.265 HCT recipients), we found 63 different PGF definitions, using various combinations of 11 common criteria. The median incidence of PGF was 7% (IQR: 5–11%, 22 cohorts). The pooled survival of PGF patients was 53% (95% CI: 45–61%, 23 cohorts). The most commonly reported risk factors associated with PGF were history of cytomegalovirus infection and prior graft-versus-host disease. Incidence was lower in studies with strict cytopenic cutoffs, while survival was lower for primary compared to secondary PGF. This work indicates that a standardized, quantitative definition of PGF is needed to facilitate clinical guideline development and to advance scientific progress.

1. Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a life-saving therapy for hematologic malignancies, bone marrow failure, red blood cell diseases, inborn errors of metabolism and severe immune deficiency, that is performed in over 40.000 patients annually [1]. Its clinical efficacy relies critically on the restoration of blood and immune cell production by the donor hematopoietic cells. Poor graft function (PGF) is a clinical syndrome characterized by persistent cytopenias, despite evidence of complete donor chimerism [2–4]. As such, PGF is distinct from graft rejection, in which donor chimerism is largely absent [5]. PGF has been reported to affect ~5% to 27% of HCT recipients and predisposes to increased risk of infections, bleeding complications and overall mortality [2,4,6–8]. The reported outcome of PGF is also variable, ranging from spontaneous recovery to long-lasting cytopenias and, in the worst case, death [9,10]. Because the reported incidence and outcome differ several-fold between studies, it remains difficult to assess the true burden of PGF after HCT and evaluate treatment strategies.

The wide range in the reported incidence and outcome of PGF may be partially explained by variability in patient cohorts and HCT strategies. Importantly, published studies also vary substantially in the criteria used to define PGF. In some studies, PGF is considered a subtype of graft failure, requiring severe cytopenias [11,12]. Contrarily, in other studies, mild cytopenias are sufficient to make a diagnosis of PGF [13,14]. Similarly, the required duration and timing of cytopenias, as well as the use of specific inclusion and exclusion criteria (e.g. the use of myelosuppressive drugs, graft-versus-host disease), differ between studies [13–16]. As a result, the severity and underlying cause of PGF may differ between studies, which could explain differences in reported incidence and outcome. To counteract this issue, both the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Transplantation and Cellular Therapy (ASTCT) have recently

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https://doi.org/10.1016/j.blre.2023.101076

Available online 22 March 2023

published definitions for PGF [3,17]. The EBMT defined PGF as "two or three cytopenias, more than two weeks after day +28, in the presence of >95% donor chimerism" [3]. In contrast, the ASTCT defines PGF as "frequent dependence on blood and/or platelet transfusions and/or growth factor support in the absence of other explanations, such as disease relapse, drugs, or infections" [17]. These consensus definitions are an important step forward towards harmonizing allo-HCT clinical practice and research. Remarkably, neither definition provides a quantitative cutoff for the depth of cytopenia required to diagnose PGF. As a result, many different definitions for PGF continue to be used. If and how these differences affect the reported incidence and outcome of PGF remains unknown.

In this systematic review, we assessed the available literature on PGF after allo-HCT, with three primary aims: (1) to generate a comprehensive overview of the various definitions of PGF that are currently being used, and of the criteria that constitute each definition; (2) to quantify the impact of these criteria on the reported incidence and (3) on the reported outcome of PGF.

2. Methods

This systematic review and meta-analysis were performed using the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. The review protocol was not registered.

2.1. Search strategy

Searches were conducted in MEDLINE, EMBASE and Web of Science databases, including hand-screen of the reference lists of the selected articles. All searches were performed from database inception until July 12th, 2022. Research questions were formulated and database-specific search strategies were developed by two authors (KFM and MEB) containing terms related to HCT and PGF (Supplementary Table 1). Records were imported into Mendeley (Elsevier) and de-duplicated by software algorithm and manual inspection.

2.2. Selection criteria

Studies were eligible if they provided (1) a definition for PGF after allogeneic HCT, and (2) included at least one patient that fulfilled those criteria. No restrictions in the observational period, publication date, or language were applied. Studies in a language not spoken by the research team were translated. Controlled trials, cohort studies, case-control studies, case series and case reports were included in the analysis of PGF definitions. Review articles and poster abstracts were excluded. To be eligible for meta-analyses of study outcome parameters, studies were also required to provide at least one of the following parameters, or data from which these parameters could be calculated: the incidence of PGF, survival of patients suffering from PGF, or risk factors associated with PGF.

2.3. Eligibility assessment, data extraction and quality assessment

Studies were screened for eligibility by title and abstract, followed by full-text screening, by two authors (KFM and MEB) independently. Data extraction was performed by one author (KFM or MEB) using an extraction table (Supplementary Table 2) and then checked by the other author. Extracted data included study information, HCT characteristics, PGF definition criteria, and outcome parameters. Quality assessment was performed by KFM and MEB for each outcome parameter separately and rated as low, intermediate, or high, based on predefined guiding questions (Supplementary Table 3), derived from the Study Quality Assessment Tools of the National Heart, Lung and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Discrepancies between authors in screening, data extraction or quality assessment were resolved through consensus.

2.4. Study outcomes and data synthesis

Study eligibility for pooled analysis of outcome parameters was based on the availability of the required parameters for that specific outcome. To calculate the incidence, the reported number of patients that experienced PGF during the study was divided by the total number of transplanted patients. Since the majority of studies did not report data on the number of HCT recipients that died between HCT and the diagnosis of PGF, we were unable to calculate a competing risk-adjusted incidence of PGF. For the outcome of survival, the numerator was the reported number of patients alive at the end of follow-up, and the denominator was the total number of PGF patients followed-up. Analysis of median survival or survival at specific time points (e.g., 1-year overall survival) was not performed, since the necessary data were only available in a limited number of studies. Risk factors for PGF were reported in tabulated form if at least two studies reported a significant difference in univariate or multivariate analysis between patients with and without PGF.

2.5. Exclusion of studies with potential overlap

For each outcome parameter, potential overlap in study cohorts, as determined by study inclusion period, inclusion center and HCT characteristics, was checked. In case of potential overlap, the study with the largest cohort was included in our analyses. In case of multiple cohorts within a single study (e.g., studies investigating the impact of different conditioning regimens on HCT outcomes), cohorts were reported separately if the outcome parameter differed significantly between cohorts, or if only specific cohorts could be included due to (potential) overlap.

2.6. Statistical analysis and visualization

All analyses were performed in RStudio [19,20] and visualized using the {ggplot2} package [21], GraphPad Prism [22] and/or Adobe Illustrator [23]. For incidence and survival outcomes, meta-analyses with random effect models were performed using the {meta} package [24]. Outlier studies were excluded if their 95% confidence interval did not overlap the 95% confidence interval of the pooled effect. Heterogeneity between studies was assessed using the Higgins & Thompson's I^2 Statistic, with an I^2 of 75% or more indicating substantial heterogeneity [25]. In case of substantial heterogeneity, median and interquartile ranges were stated. Subgroup analyses based on cutoff values for individual definition criteria were performed using mixed-effect models in the {meta} package, without a common estimate of τ^2 (the variance of the distribution of true effect sizes) across subgroups [24]. In the case of multiple cutoff values, all values other than the most strict cutoff were grouped. *P*-values for subgroup differences were based on Cochran's Q test, and *p*-values below 0.05 were considered statistically significant.

2.7. Data sharing

Overviews of the included studies and their characteristics are provided in Supplementary table 4. The complete dataset generated in this study is available upon request.

3. Results

3.1. Study selection

In total, 797 records were identified in the search (Fig. 1). After de-duplication and removal of poster abstracts, 209 articles were screened on title and abstract. Out of 111 articles screened on full text for eligibility, 40 articles were excluded because they did not provide a definition for PGF. Two articles were excluded because they concerned

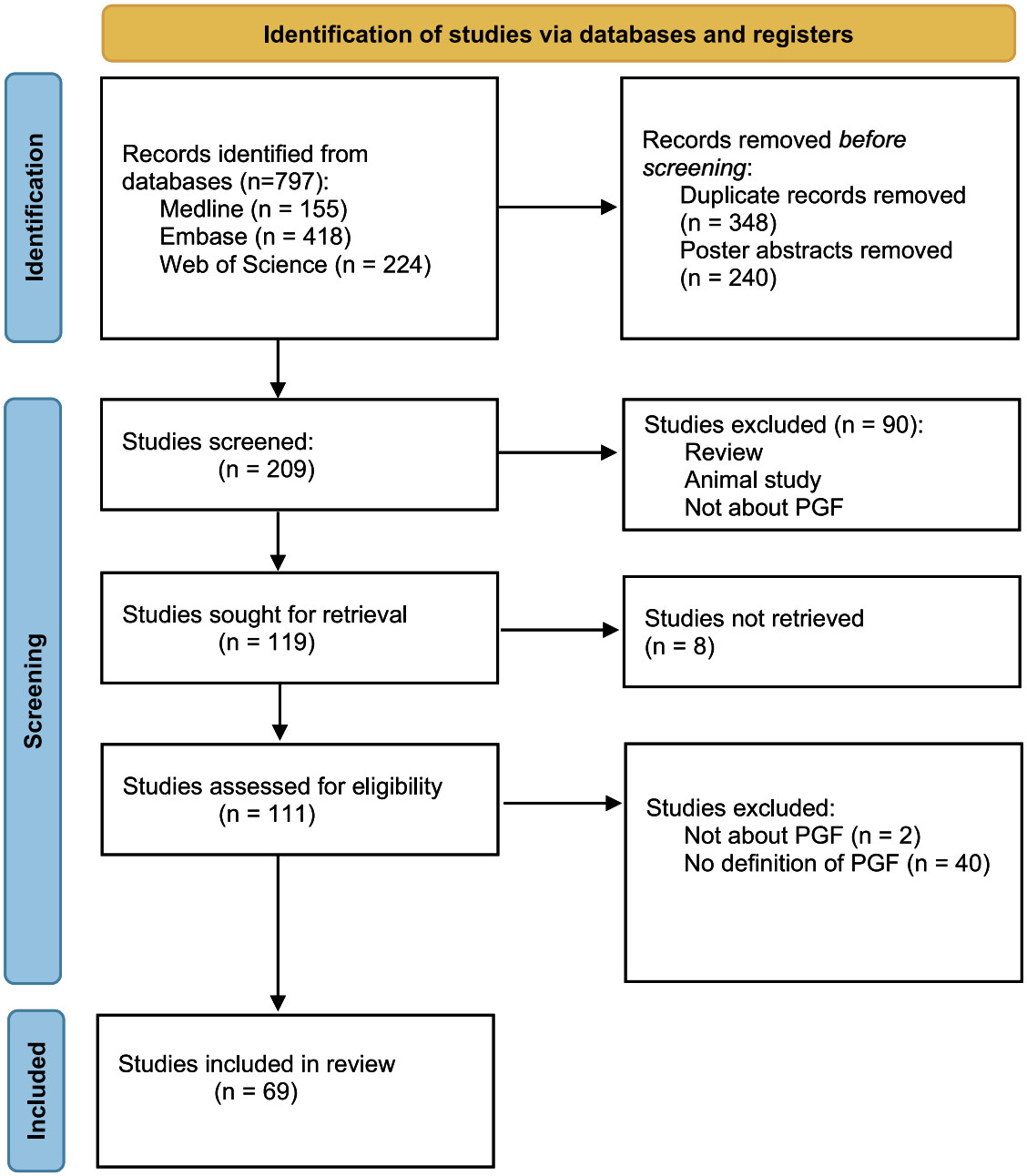

Fig. 1. Flowchart of literature search. Based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18].

primary graft failure instead of poor graft function. A total of 69 studies satisfied all inclusion criteria and were used in further analyses [7–16,26–84].

3.2. Characteristics of included studies

Characteristics of the included studies are summarized in Supplementary table 4. Most studies were conducted in Asia (41 studies, 59%), followed by Europe (21 studies, 30%) and North America (5 studies, 7%). The total number of transplanted patients in individual studies ranged from 1 to 1996, and the number of PGF patients ranged from 1 to 106. Underlying diseases in study cohorts were hematological malignancies (38 studies, 55%), bone marrow failure (11 studies, 16%), or a variety of different diseases (20 studies, 29%). Studies were conducted in adults (aged above 16 years) in 37 studies (54%), in pediatric patients (aged below 20 years) in 4 studies (6%) and a combination of both pediatric and adult patients in the remaining 28 studies (41%).

3.3. Aim 1: Criteria used to define PGF

In total, 11 criteria were identified that were used to define PGF in more than one study (Fig. 2A). A neutrophil cutoff was the most commonly included criterion ($n = 62$, 90%), followed by a thrombocyte cutoff ($n = 60$, 87%) and requirements for donor chimerism ($n = 58$, 84%). Criteria involving the timing of cytopenias, including the time of onset (56%), duration (48%) and a distinction between primary and secondary PGF (49%), were included in the fewest definitions. The median number of PGF criteria that was included in a definition was 8 (IQR 6–10) (Fig. 2B). Among the 62 definitions that include a cutoff for neutrophils, 44 (71%) used a cutoff of 0.5×10^9/L, eleven (18%) a cutoff of 1.0×10^9/L and seven (11%) a cutoff of 1.5×10^9/L (Fig. 2A). Likewise, cutoffs for thrombocytes and hemoglobin were variable

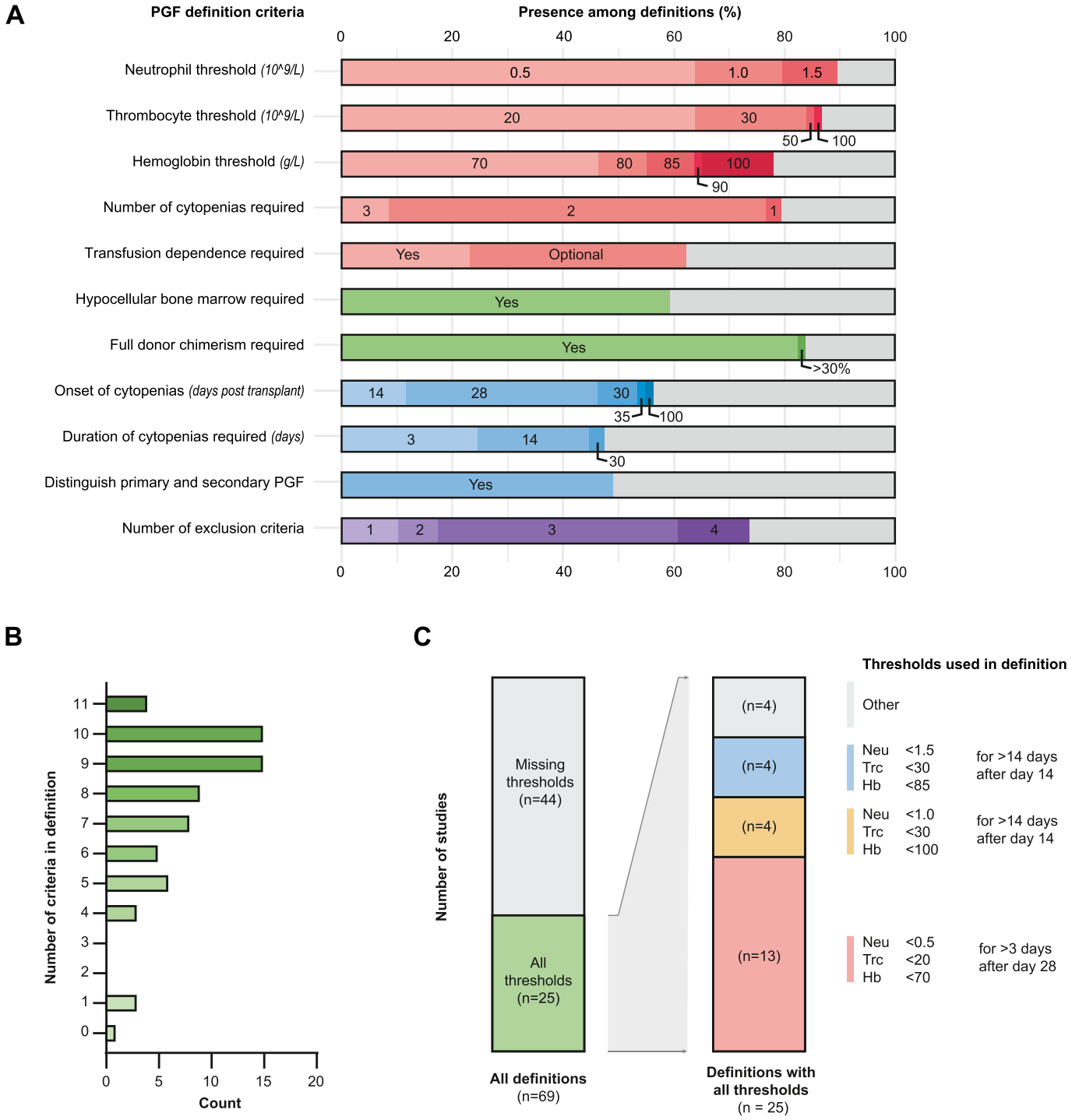

Fig. 2. Definitions for poor graft function show large heterogeneity in the number and manner in which criteria are used. A) Stacked bar plot demonstrating the eleven different criteria that were used to define poor graft function (PGF) in at least two studies. Criteria relating to cytopenia severity are indicated in red, bone marrow in green, timing of cytopenias in blue and exclusion criteria in violet. If applicable, different cutoff values or levels of each criterion are shown, along with the proportion of definitions in which the specific criterion was present. Gray bars indicate the criterion was not reported. Exclusion criteria include concurrent graft-versus-host disease, relapse, active infection, and drug-induced myelosuppression. B) Histogram of the frequency at which a given number of criteria was used in a definition of PGF, with a median of 8 criteria per definition. C) Among the 25 definitions that reported a cutoff for neutropenia, thrombocytopenia, anemia, duration of PGF and timing of PGF, three combinations of cutoffs appeared in 13, 4 and 4 definitions, respectively. Abbreviations: PGF: poor graft function; Neu: neutrophils, Trc: thrombocytes; Hb: hemoglobin. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

among studies (Fig. 2A). Together, the inclusion or exclusion and different values for these 11 criteria resulted in 63 distinct definitions for PGF.

Focusing on definitions in which cutoff values for cytopenic depth, timing and duration were mentioned, we noted that specific values were often used in set combinations. For example, 13 studies (52%) defined PGF by neutrophils below 0.5×10^9/L, thrombocytes below 20×10^9/L and hemoglobin below 70 g/dL for three consecutive days after day 28

post-HCT (Fig. 2C). Among these studies, Kong and colleagues were the first to report these cutoff values [15]. Similarly, 4 studies (16%) used the same cutoffs for PGF as Stasia et al. [73], while another 4 studies (16%) followed cutoffs from Klyuchnikov and colleagues [14] (Fig. 2C). These three distinct definitions may have served as templates from which other, similar definitions have arisen, either by incomplete adaptation or the combination of criteria from different key articles.

3.4. Aim 2: the impact of definition criteria on the incidence of PGF

Twenty-two cohorts could be used in the meta-analysis on the incidence of PGF (Fig. 3A). Quality of these studies was assessed as high in 9 studies (41%), intermediate in 8 studies (36%) and low in 5 studies (23%, Supplementary table 5). Overall, these studies report a median incidence of PGF of 0.07 (IQR: 0.05–0.11%). Due to the substantial heterogeneity between observed incidences (I^2 = 78%), a reliable pooled incidence could not be calculated.

We hypothesized that the use of higher, more lenient cytopenia cutoffs would result in a higher reported incidence of PGF. Subgroup analysis revealed that studies that used a strict neutrophil cutoff of 0.5 × 10^9/L showed a lower pooled incidence of PGF compared to studies using more lenient cutoffs (0.06 versus 0.10, p = 0.02, Fig. 3B). Similarly, the incidence of PGF was lower in studies that used thrombocyte cutoffs of 20 × 10^9/L (0.07 versus 0.11, p < 0.01) and hemoglobin cutoffs of 70 g/L (0.06 versus 0.10, p < 0.01) compared to studies using higher cutoff values (Fig. 3C-D). It is important to note that the most stringent cutoff values were often used together. As a result, the impact of cutoffs for individual blood cell lineages is difficult to interpret.

Regarding its dynamics and onset, PGF can be categorized into two mutually exclusive subtypes. In primary PGF, blood counts never reach the defined cutoff values, while in secondary PGF, blood counts drop below the cutoffs after initial recovery from aplasia. These two PGF subtypes are reported to have different incidence, survival, and, possibly, different pathophysiology [4,54,74]. In subgroup analysis, the

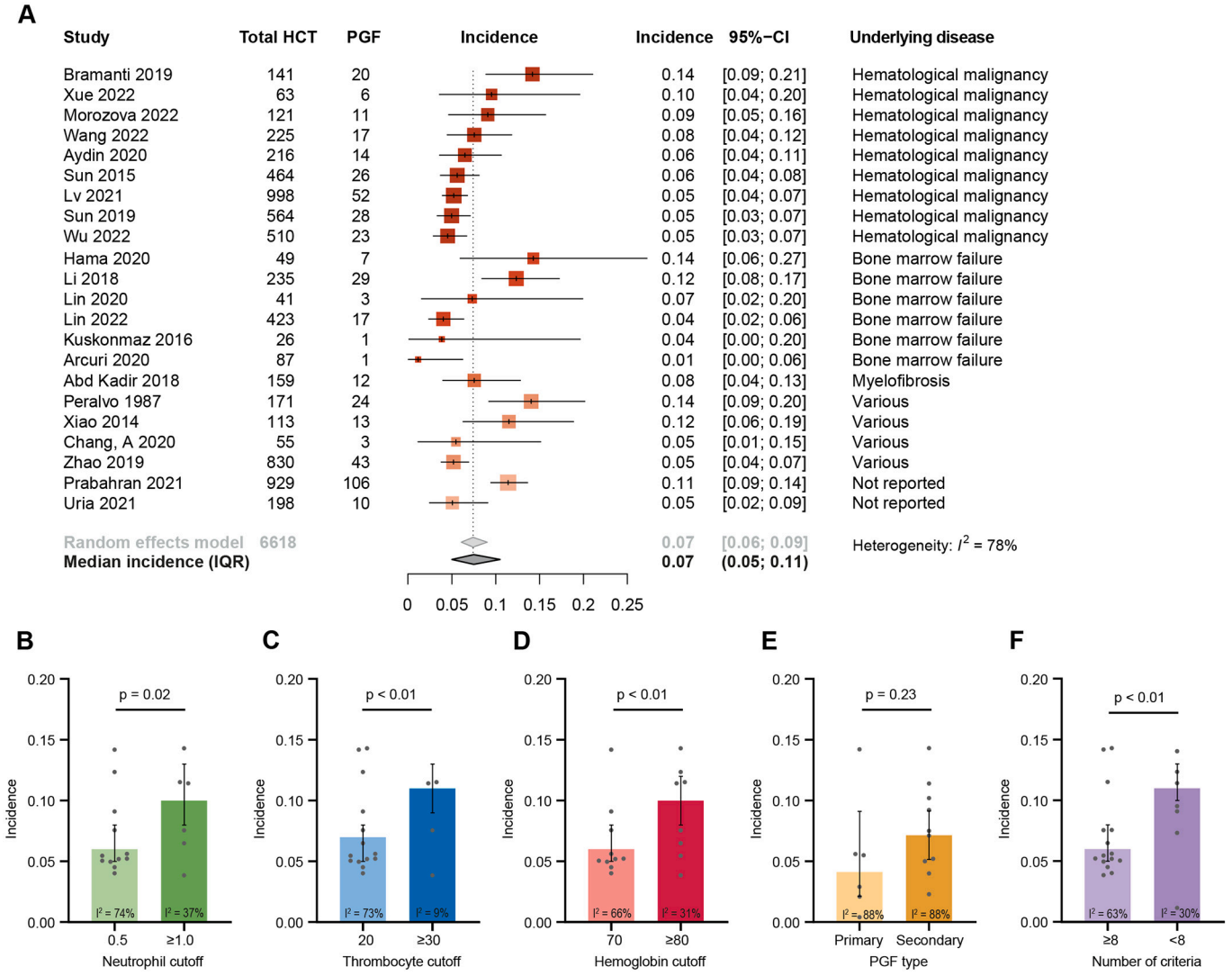

Fig. 3. Incidence of poor graft function after stem cell transplantation. A) Forest plot showing the incidence of poor graft function (PGF), as well as 95% confidence intervals, in 22 cohorts, defined as the proportion of patients with PGF within the total number of transplanted patients. Cohorts are arranged by underlying disease and decreasing incidence. Study weight, based on inverse variance, is demonstrated by the size of the red square. Because of substantial heterogeneity, both pooled incidence and median incidence with interquartile range are reported. B—F) Subgroup analyses, based on different aspects of the definition, as depicted on the X-axis. Pooled incidence as well as 95% confidence intervals are shown for B,C,D and F. Because of substantial heterogeneity, median incidence with interquartile range is reported in E. For B-E, cohorts were only included in the subgroup analysis if the respective criterion was mentioned in the definition. For F, the median number of criteria among all definitions was used as a cutoff. Depicted p-values are based on Cochran's Q test for subgroup differences using a mixed effects model. Abbreviations: HCT: hematopoietic stem cell transplantation, CI: confidence interval, IQR: interquartile range. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reported incidence of these two PGF subtypes remained heterogeneous and no significant differences were observed. The median incidence of primary PGF was 0.04, (IQR: 0.02–0.06) compared to 0.07 for secondary PGF (IQR: 0.05–0.10, $p = 0.23$, Fig. 3E). Subgroup analysis, based on the required duration of PGF, or the time after HCT at which PGF was measured, did not show any significant difference (data not shown).

The reported incidence of PGF may also be related to the number of criteria used in its definition. Therefore, the reported incidence was compared between studies with at least 8 criteria in their definition to those with <8, as 8 is the median number of definition criteria among all studies (Fig. 1B). The pooled incidence was higher in studies that reported <8 criteria (0.11 versus 0.05, $p < 0.01$, Fig. 3F), again indicating that strict selection of PGF patients results in lower incidence.

Notably, a negative correlation was found between the incidence of PGF and the year in which the study cohort was initiated, with recent cohorts showing a lower incidence of PGF (Supplementary fig. 1). This may reflect improvements in the HCT procedure over time or, alternatively, changes in the definitions for PGF over time. Subgroup analysis based on the underlying disease of the study cohorts showed no significant differences and heterogeneity within subgroups remained substantial (data not shown).

3.5. *Aim 3: the impact of definition criteria on the survival of PGF patients*

Twenty-three cohorts from twenty-two different studies reported on the survival of PGF patients, either after standard of care or after specific treatment, and could be used in the meta-analysis. The quality was assessed as high in 5 cohorts (22%), intermediate in 11 cohorts (48%) and low in 7 cohorts (30%, Supplementary table 6). Four studies overlapped with those included in the meta-analysis on the incidence of PGF. Time at which overall survival (OS) was assessed was infrequently mentioned, and if it was, time points differed between studies, ranging from 1 to 5-year OS. Therefore, the percentage of patients alive at last follow-up was reported here (Fig. 4A). Among a total of 566 PGF patients, pooled survival was 53% (95% CI: 47–59%). Subgroup analysis based on PGF treatment revealed no significant differences ($p = 0.31$, data not shown).

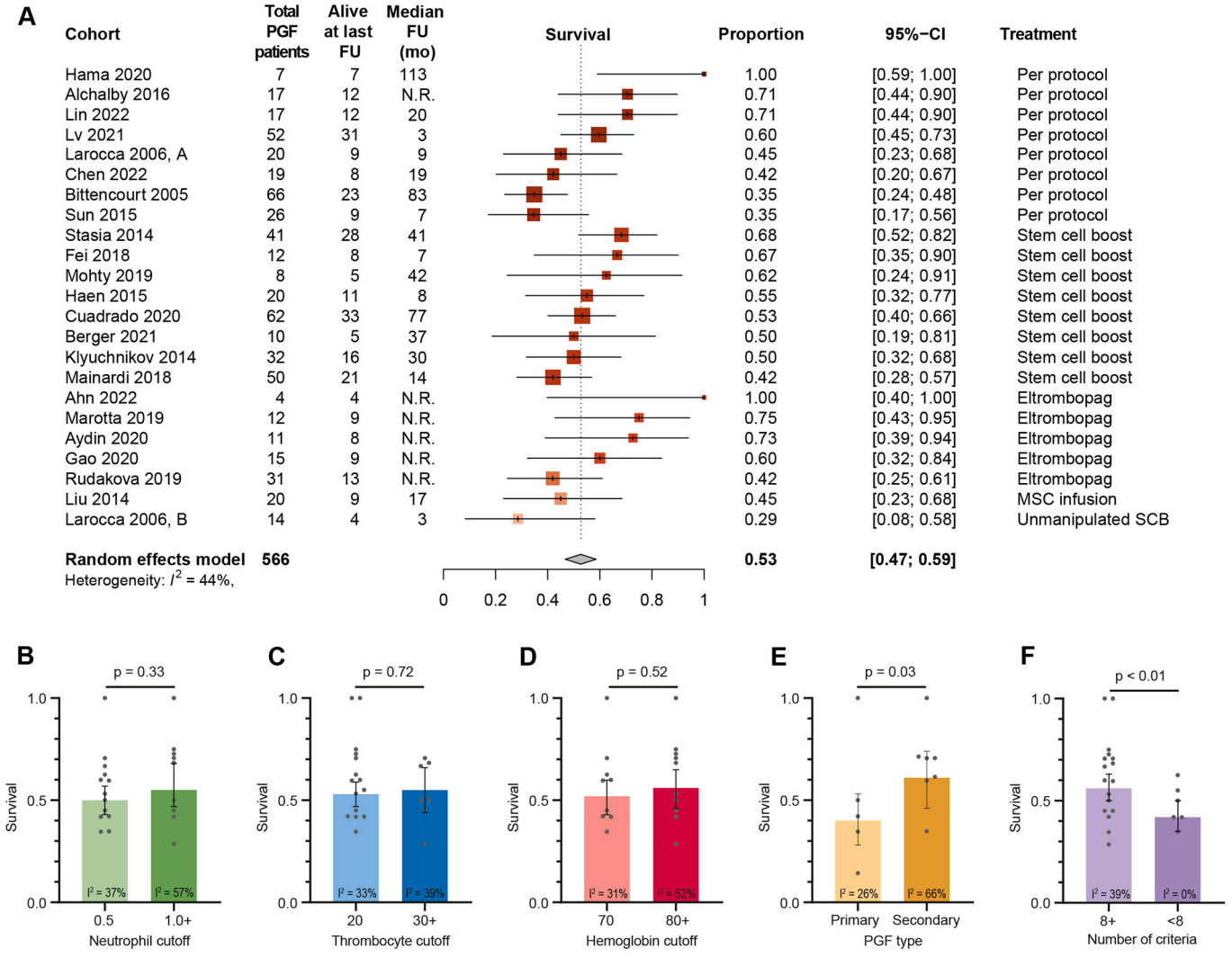

Fig. 4. Survival of patients suffering from poor graft function. A) Forest plot showing the survival of 23 cohorts of poor graft function (PGF) patients, defined as the proportion of patients alive at last follow-up, as well as 95% confidence intervals. Cohorts are arranged by treatment type and decreasing survival. Study weight, based on inverse variance, is demonstrated by the size of the red square. B—F) Bar plot visualisations of subgroup analyses, based on different aspects of the definition, as depicted on the X-axis. Pooled survival as well as 95% confidence intervals are shown. For B-E, cohorts were only included in the subgroup analysis if the respective criterion was mentioned in the definition. For F, the median number of criteria among all definitions was used as a cutoff. Depicted *p*-values are based on Cochran's Q test for subgroup differences using a mixed effects model. Abbreviations: PGF: poor graft function, FU: follow-up, mo: months, CI: confidence interval, N.R.: not reported, SCB: stem cell boost. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Potential risk factors for poor graft function. Overview of potential risk factors for PGF that were found to be significant in at least two different studies. Columns (left to right) show the potential risk factor, the number of studies that reported results for that risk factor, the number of studies in which that risk factor was found to be correlated to PGF, the percentage of reporting studies in which the risk factor was significant, and individual study data. Abbreviations: CMV: cytomegalovirus, GvHD: graft-versus-host-disease, HLA: Human leukocyte antigen, CD34: cluster of differentiation 34, –: not reported, ns: not significant, ✓: significant in univariate analysis, ✓✓: significant in multivariate analysis.

Potential risk factors	Tested in # studies	Predictive in # studies	Percentage	Bramanti 2019	Chang 2020	Sun 2015	Chen 2022	Zhao 2019	Kong 2016a	Alchalby 2016	Hama 2020	Lv 2021	Prabahran 2021	Sun 2019	Kong 2013	Lin 2022	Shi 2017	Peralvo 1987	Xiao 2014	Wang 2016	Song 2018	Wu 2022	Morozova 2022
History of CMV	13	5	38%	–	–	–	ns	✓	ns	–	ns	✓✓	✓	✓✓	ns	ns	–	–	✓✓	ns	ns	–	–
History of GvHD	13	5	38%	–	–	–	ns	ns	ns	ns	–	✓✓	✓	✓	✓	✓	–	–	ns	ns	ns	–	–
Splenomegaly	3	3	100%	–	–	–	✓✓	✓✓	–	✓	–	–	–	–	–	–	–	–	–	–	–	–	–
Donor-recipient																							
Relatedness	9	3	33%	–	–	–	✓✓	ns	–	ns	ns	✓	ns	–	ns	–	✓	–	ns	–	–	–	–
Major bloodgroup mismatch	18	3	17%	ns	ns	ns	✓	ns	ns	ns	–	ns	–	ns	ns	ns	✓	ns	✓✓	–	ns	ns	ns
High recipient age	19	3	16%	ns	ns	ns	–	ns	ns	✓	–	ns	ns	ns	ns	ns	✓	ns	✓✓	ns	ns	ns	ns
High serum ferritin	4	2	50%	–	–	–	ns	✓✓	–	–	–	–	–	–	–	ns	✓	–	–	–	–	–	–
History of other viral reactivation	6	2	33%	–	–	–	–	–	–	–	ns	✓	✓	✓✓	–	ns	–	–	ns	ns	–	–	–
HLA mismatch	15	2	13%	ns	ns	✓	–	–	ns	ns	ns	✓	–	–	ns	ns	ns	ns	ns	ns	ns	–	–
Low CD34+ cell-dose	16	2	13%	ns	ns	ns	ns	✓✓	ns	–	–	ns	ns	✓✓	ns	ns	ns	–	ns	ns	–	ns	–
Donor source	3	0	0%	ns	–	–	–	–	–	–	–	–	–	–	–	–	–	–	ns	–	–	–	ns
Study characteristics																							
Primary vs secondary				1	1	1	1	1	1	2	2	2	2	2	2	2	1 + 2	–	–	–	–	–	–

Again, the potential effects of individual PGF criteria on survival were investigated. In contrast to their association with incidence, higher cytopenic cutoffs were not associated with improved survival (Fig. 4B-D). Instead, the subtype of PGF appeared to affect survival: survival of primary PGF patients was 40% (95% CI: 28–53%), compared to 61% for secondary PGF (95% CI: 46–73%, $p = 0.03$, Fig. 4E). The required duration or timing at which PGF was measured did not correlate to the reported survival (data not shown). Unexpectedly, cohorts with a more complete definition, defined as at least 8 PGF criteria, showed higher survival compared to cohorts that included <8 criteria in their definition (56% versus 42%, $p < 0.01$, Fig. 4F), indicating that the inclusion of more criteria in the definition for PGF does not select for patients with more severe PGF.

Since the survival of HCT recipients differs depending on their underlying disease, we hypothesized that the underlying disease may also be an important determinant of survival in patients with PGF. Subgroup analysis based on underlying disease did not show any significant differences (data not shown). However, this analysis was hampered by the low number of studies investigating the survival of PGF patients in the context of a specific disease (Supplementary table 6). In addition, neither the year of study start, nor the duration of follow-up was associated with survival of PGF patients (Supplementary figs. 2 and 3). For both the incidence and survival of PGF, sensitivity analyses were performed by excluding either all low-quality studies, or studies including only pediatric patients (Supplementary table 7), which did not affect our conclusions.

3.6. Risk factors for PGF

Risk factors for PGF were assessed in twenty studies. Quality of these studies was assessed as high in 11 studies (55%), intermediate in 7 studies (35%) and low in 2 studies (10%, Supplementary table 5). Table 1 shows the ten risk factors for PGF that were significant in uni- or multivariate analysis in at least two independent studies. The potential risk factors investigated differed per study, with no study investigating all ten potential risk factors. History of cytomegalovirus (CMV) infection and history of graft-versus-host disease (GvHD) were investigated in 13 studies and found to be associated with PGF in 5 studies (38%) each. History of GvHD was only identified as a risk factor for secondary PGF. Contrastingly, high serum ferritin (2/4 studies, 50%) was identified as a risk factor only in studies investigating primary PGF patients. Other identified risk factors included splenomegaly (3/3, 100%), an unrelated donor (3/9 studies 33%), major blood group mismatch (3/18 studies, 17%) and higher recipient age (3/19 studies, 16%). Stem cell source (bone marrow peripheral blood, or both) was not associated with the incidence of PGF in any of the three studies investigating this potential risk factor (Table 1). Importantly, the heterogeneity of the HCT cohorts, potential risk factors tested, as well as the heterogeneous definitions for PGF makes it difficult to pool these data. In addition, these studies focus on associations between clinical observations and PGF, which does not indicate causality. Both homogeneous clinical studies and fundamental studies are required to unravel the underlying mechanisms by which these potential risk factors may lead to PGF.

4. Discussion

This systematic review and meta-analysis show that (1) large heterogeneity is present in the criteria used to define PGF after allo-HCT. Differences were found in the cutoff values to define cytopenia, the time after HCT at which these were measured, their duration and the inclusion or exclusion of specific risk groups. Importantly, these differences were associated with differences in the reported incidence and outcome of PGF; (2) studies using strict cytopenic cutoff values generally report a lower incidence of PGF compared to those using a more lenient cutoff; and (3) while not all definitions distinguish between primary and secondary PGF, this difference has important consequences

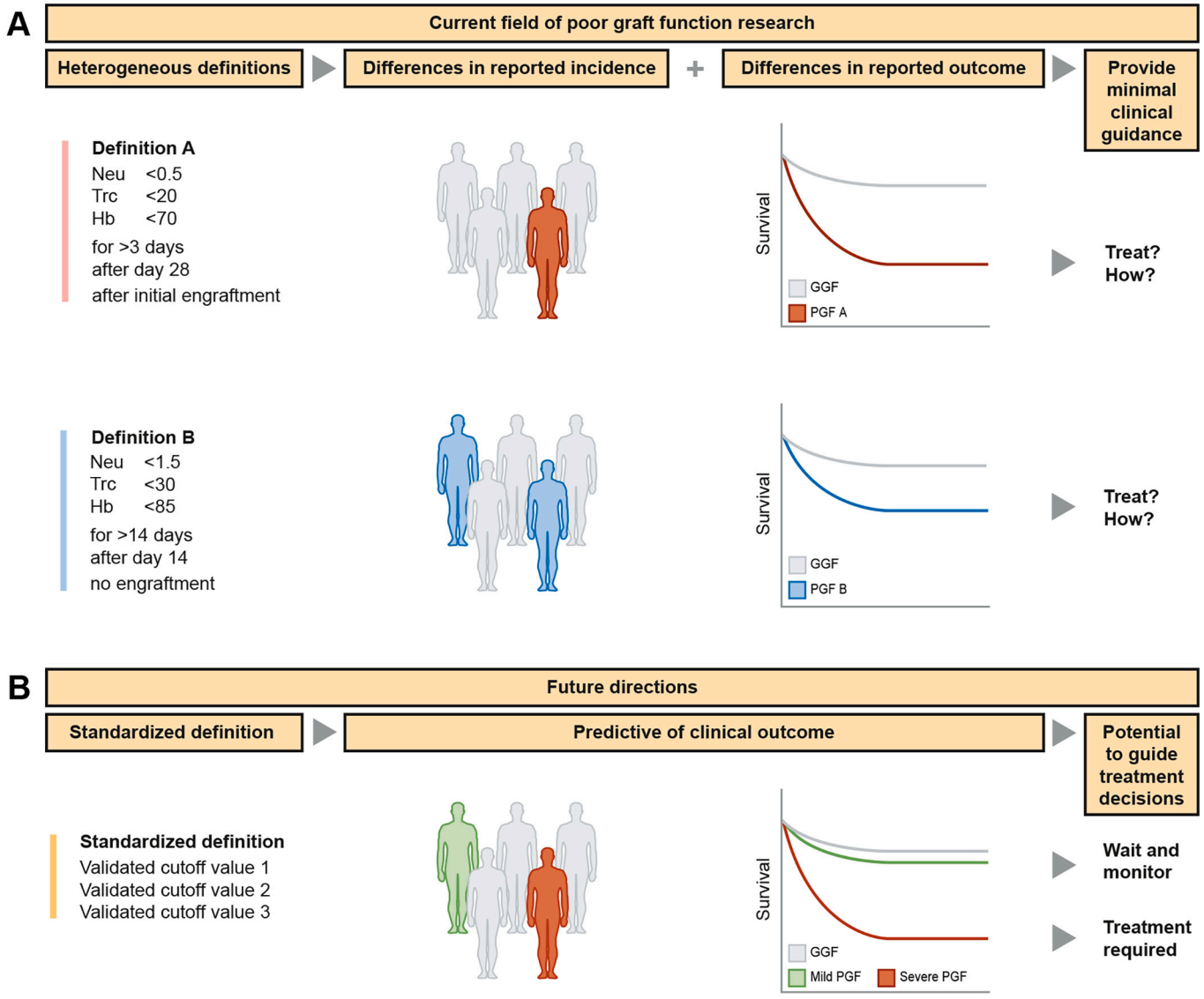

Fig. 5. Visual representation of study results. A) Currently, different definitions for poor graft function coexist. These differences affect reported incidence and outcome, and inhibit the aggregation of study results into clinical guidelines. B) A standardized definition for PGF that uses routinely measured parameters and validated cutoff values predictive of clinical outcome will advance scientific understanding and aid clinical decision making.

for patient survival. Our results have several clinical and scientific implications.

First, our data stress the importance of reporting the specific criteria used to define PGF, and of taking these criteria into account while interpreting scientific literature. Studies that evaluate preventive or therapeutic strategies for PGF often compare their results to those reported in literature [31,41,43,82]. Given that the PGF definition affects its observed incidence and outcome, an accurate comparison of results requires selecting studies using similar definitions. Regrettably, reporting of PGF criteria is commonly incomplete (Fig. 2A). For instance, 15 out of 69 included studies (22%) did not specify their cutoff value for neutrophils, thrombocytes or hemoglobin. In addition, among the 111 articles screened in this study, 20 articles reported on PGF patients without providing a definition. To enable correct interpretation and comparison of results, studies on PGF should at least report the following aspects: the cutoff values used to define cytopenia, the number and duration of cytopenias used to define PGF, the time after HCT at which cytopenias were measured (also splitting patients into primary and secondary PGF), and the inclusion or exclusion of specific risk groups (e.g., patients with GvHD).

Second, our data urge for a *standardized* definition of PGF. Currently, the concurrent use of different definitions prevents the aggregation of results from individual studies. This in turn hampers the development of evidence-based clinical guidelines (Fig. 5A). Important initiatives towards standardization have recently been published by the EBMT and ASTCT [4,17]. Notably, these definitions differ in several aspects and still allow for considerable variability, for instance in the required cytopenic depth. In clinical practice, some flexibility in the management of PGF may be warranted, since acceptable depth and duration of cytopenias may differ per patient, depending on characteristics such as bleeding risk or concurrent disease. However, from a scientific perspective, international consensus on a standardized, quantitative definition of PGF is paramount to advance scientific and clinical progress.

Third, our data support the existence of different subtypes of PGF, with different etiology, outcome, and which may require different treatment [3]. Ultimately, PGF is the clinical manifestation of the insufficient output of hematopoietic progenitor cells, resulting in anemia, thrombopenia, and/or poor immune function. Its underlying pathophysiology is likely multifactorial, including HSC-related, niche-

related and environmental factors, that affect one (isolated cytopenia) or more (PGF) hematopoietic lineages. Clinical risk factors may provide hints towards potential causes of PGF and may guide fundamental studies investigating the underlying mechanisms. In this work, we show that the most commonly reported risk factors correlated with PGF are a history of GvHD and viral reactivations post-HCT. These findings are in line with various recent studies, which demonstrate that inflammation, in particular IFN-γ signalling, can have detrimental effects on both HSCs and niche cells [85–87]. Other identified risk factors, such as a low splenomegaly, may increase the likelihood of PGF through different pathogenic mechanisms. These factors may reduce the number of HSPCs homing to the bone marrow, scavenge differentiated blood cells, or serve as an indicator of previous tissue damage, including damage to the bone marrow niche. Careful discrimination and selection of specific subgroups of PGF patients will advance fundamental studies aiming to dissect the underlying mechanisms leading to PGF.

The identification of subgroups of PGF with specific etiologies may in turn have important clinical consequences. For instance, prophylactic treatment of patients at high risk of niche-mediated PGF (based on low numbers of bone marrow endothelial cells) with *N*-acetyl-L-cysteine resulted in a significant reduction of the incidence of PGF and isolated thrombocytopenia [12]. Similarly, the efficacy of common treatments for PGF, including CD34+ selected stem cell boost or thrombopoietin-receptor agonists, may depend on the underlying etiology of PGF [62,75,90]. By improving the homogeneity of patient cohorts in clinical and fundamental studies, a standardized, quantitative PGF definition may aid in the identification of subgroup-specific etiologies and treatments.

4.1. Strengths and limitations

This review has several strengths. It is one of the few systematic reviews and meta-analyses on PGF after allo-HCT, and the first to provide pooled estimates on its incidence and outcome. Existing reviews are generally narrative and focus on the pathophysiology of PGF. Using a systematic approach, we provide a comprehensive overview of existing literature. Although the need for a consistent definition of PGF has been raised by others [3,4], the consequences of the lack of such a definition have not been studied before. Our findings indicate that the reported incidence of PGF may differ twofold, depending on the cutoff values for neutrophils, thrombocytes or hemoglobin, and highlight the importance of distinguishing between primary and secondary PGF. Importantly, many of the issues regarding heterogeneity in definitions and outcomes of PGF may also apply to HCT with autologous cells.

Our study contains some limitations. First, due to the unavailability of individual patient data, our meta-analysis was limited to aggregate data of the cohorts. While we were able to demonstrate some of the effects of definition criteria on the incidence and outcome of PGF, the true effects of cytopenic depth, duration and onset may be more profound. *Re*-analysis of large retrospective cohorts for which all blood counts are available may shed light on the exact correlation between PGF severity and outcome.

Second, clinical characteristics, such as underlying disease, conditioning, donor source and PGF treatment, were very heterogeneous both within and between studies. At the study level, subgroup analyses on the underlying disease and PGF treatment did not show any significant differences. However, we could not assess the effects of these clinical characteristics on PGF at an individual level. Larger studies with homogeneous cohorts are necessary to compare the incidence and outcome of PGF between patients with different diseases or transplanted from different donor sources.

Third, our list of clinical risk factors for PGF may not be exhaustive, due to our decision to report only risk factors correlated with PGF in at least two studies. On the other hand, our findings may suffer from reporting bias, as studies that did not find an association between clinical parameters and PGF, may not have published their results.

Lastly, outcome parameters were reported differently between studies. While the incidence of PGF is affected by the number of patients that die before PGF is measured, few studies reported these numbers and competing-risk analysis could not be performed. Similarly, due to large differences in the manner and timepoint at which survival was measured, estimates of 1-year or 5-year overall survival could not be calculated. The incidence and survival proportions in this review provide the first estimates for the overall incidence and outcome of PGF. However, the use of competing risk and time-to-event analyses in large patient cohorts may provide more accurate estimates in the future.

5. Future considerations

With the increasing use and improved survival of HCT, the number of HCT recipients with PGF is expected to grow substantially in the coming decades. To understand the true burden of PGF and to gain insight into its etiology, a quantitative and standardized definition of PGF is required. Ideally, this definition would fulfil a number of criteria (Fig. 5B). First, it should be easily applicable in clinical and scientific practice. To this end, the definition should use parameters that are routinely measured in clinical practice and/or registered in clinical databases. Second, it should be unambiguous, explicitly stating cutoff values for the required number, duration and severity of cytopenias, distinguish between primary and secondary PGF, and list specific exclusion criteria. Third, a standardized definition should be clinically relevant, clearly discriminating between patients with favorable versus poor prognoses (e.g., requiring re-transplantation), or between those more or less likely to benefit from therapeutic interventions (e.g., stem cell boost). Currently, cutoff values are often based on expert opinion, which may explain the use of different cutoffs between studies. Instead, existing datasets of post-transplantation blood counts could be used to establish data-driven cutoff values that identify patients at risk of long-term graft dysfunction that are likely to require therapeutic intervention. Such analyses may also identify new markers that could aid in the identification of high-risk PGF patients. For example, early CD4+ T cell immune reconstitution, which has been linked to increased survival of HCT and GvHD [88,89], may provide additional information besides neutrophils, thrombocytes and hemoglobin values alone.

Importantly, hematopoietic recovery and engraftment kinetics may be influenced by multiple factors, including donor type, stem cell source, cell manipulation and dose, underlying disease, GvHD-prophylaxis and conditioning intensity [12,52,91–93]. To deal with this heterogeneity and still identify patients with favorable or poor prognosis, distinct cutoff values could be established for specific transplantation settings. In the long term, advances in data analysis and modelling, combined with artificial intelligence, may enable real-time analysis of blood counts, predicting future trajectories for individual patients based on existing data and enable early identification of patients at risk of poor outcome.

6. Practice points

- Studies and clinical outcome assessments should explicitly state the criteria used to define PGF
- When interpreting and comparing evidence on PGF, readers should consider the definition used

7. Research agenda

- Identify clinically relevant PGF criteria based on existing datasets
- Translate these evidence-based criteria into an international consensus definition for PGF
- Investigate the incidence and outcome of PGF in the setting of specific underlying diseases or donor sources
- Use precise definitions to investigate the pathophysiology of PGF in carefully selected patient cohorts

Funding

The KiKa project grant supported the salary of KFM. The funders had no role in the design, execution or writing of this work, nor in the decision to submit results.

Authorship contributions

Conceptualization: All authors. Study search, study selection, data extraction and quality assessment: KFM and MEB. Data analysis and figures: KFM. Writing (original draft): KFM and MEB. Writing (review and editing): All authors. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

CAL is on a data and safety monitoring board for ExCellThera and was medical advisor for Sobi and Orchard Therapeutics. SN was advisor for Sobi.

Acknowledgements

This study was financially supported by a VENI grant of the Netherlands Organization for Scientific Research (NWO) (grant number VI.Veni.202.021 to MEB), a physician scientist grant of the European Hematology Association (to MEB), a John Hansen research grant from the DKMS and a KiKa project grant (project number 418).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.blre.2023.101076.

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