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RESEARCH ARTICLE

Assessment of monocytic-myeloid-derived suppressive cells (M-MDSC) before and after allogeneic hematopoietic stem cell transplantation in acute leukemia patients

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Abstract

In this monocentric prospective study, the influence on long-term outcomes of peripheral blood levels of monocytic-myeloid-derived suppressive cells (M-MDSC) was investigated in 56 patients with acute leukemia (myeloid $n = 47$; lymphoid $n = 9$) before and after (Days+60/+90) allogeneic hematopoietic stem cell transplantation (Allo-HSCT). A risk of relapse was found to be associated with a level of pregraft M-MDSC above 1.4% by ROC curve analysis. In multivariate analysis, this threshold retained a strong statistical significance (HR: 5.94 [2.09–16.87], $p = 0.001$). Considering only the group of patients who were in complete remission prior to Allo-HSCT ($n = 44$), a significant prediction of relapse was found to be associated, in multivariate analysis, with a level of pregraft M-MDSC above 1.4% (HR: 55.01 [14.95–202.37], $p < 0.001$) together with pregraft-positive measurable -residual disease (MRD) (HR: 11.04 [1.89–64.67], $p = 0.008$). A poorer OS (HR: 6.05 [1.24–29.59], $p = 0.026$) and disease-free survival (HR: 6.52 [1.41–30.19], $p = 0.016$) were also associated with higher levels of pregraft M-MDSC. Remarkably, no relapse occurred in patients with pregraft-negative MRD and ≤1.4% of M-MDSC (vs. a 3-year relapse rate of 60% for others, $p = 0.004$). Patients developing grade 3–4 acute graft-versus-host-disease (GVHD, median occurrence: day+30 posttransplant) showed significantly higher levels of M-MDSC% at days +60 and +90, suggesting a possible amplification of these immunosuppressive cells as a reaction to GVHD. In conclusion, this prospective study demonstrates a negative impact of higher proportions of peripheral M-MDSC before Allo-HSCT in leukemic patients. This paves the way to potential therapeutic intervention to decrease M-MDSC levels before Allo-HSCT and thus perhaps the incidence of relapse in such patients.

KEYWORDS
ALL, Allo-HSCT, AML, diagnosis, MDSC, monocytes, survivals

1 | INTRODUCTION

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells able to suppress innate and adaptive immune responses [1, 2]. Characterized by the typical $CD11b^+CD33^+HLA\text{-}DR^{-/low}$ immunophenotype, MDSCs in humans comprise two main subsets, namely granulocytic or polymorphonuclear (Gr- or PMN-MDSCs), expressing also CD15 and CD66b, and monocytic (M-MDSCs), expressing also CD14. A third subpopulation, called early MDSCs (eMDSCs), expresses neither CD15 nor CD14 [3]. As it is difficult to distinguish between PMN-MDSCs and neutrophils which have a similar immunophenotype, M-MDSCs are the preferably studied cell subtype.

Under abnormal conditions and through the action of various cytokines and microenvironmental factors, M-MDSC can accumulate and inhibit the functions of different cell types, such as T cells, natural killer cells, dendritic cells, and macrophages, while promoting the proliferation and differentiation of Tregs and tumor-associated macrophages [1, 2]. Due to these immunosuppressive properties, they have been associated with the progression/chemoresistance of various solid tumors [4, 5], by impairing efficient antitumoral immune responses. This is likely to be also the case for hematological malignancies [6–8]. In this context, we have recently reported that a percentage of peripheral blood (PB) M-MDSC higher than 0.55% of leukocytes at diagnosis and a decrease of M-MDSC% after induction chemotherapy both stand as independent negative prognostic factors for leukemia-free (LFS) and overall (OS) survival in acute myeloid leukemia (AML) patients [9].

Alternatively, MDSCs can also have a positive effect as part of their paradoxical dual functionality depending on the microenvironment and the situation in which these cells grow [2]. For example, some studies have shown an antitumor effect through increased phagocytosis and cytokine production [2]. In the context of allogeneic hematopoietic stem cell transplantation (Allo-HSCT), it has also been reported that MDSCs may have a protective role against acute and chronic GVHD [10–13], especially when they are found in high proportion in the graft infused or in the recipient peripheral blood (PB) after transplant [14]. There is however only very limited knowledge about their ability to preserve the graft-versus-leukemia effect [15].

The present study focused on the impact of peripheral levels of M-MDSC on posttransplant outcomes in a cohort of adult patients with acute (both myeloid, AML, or lymphoid, ALL) leukemia who benefited from an Allo-HCST.

2 | METHODS

This work represents the second part of a monocentric prospective study, the first part of which was published by our group in 2022 [9]. The latter reported the influence of peripheral M-MDSC levels at diagnosis and after intensive induction chemotherapy in adult patients with AML or ALL [9]. Here, the potential impact of M-MDSC peripheral percentages was investigated before and after Allo-HSCT on several outcomes, that is, acute and moderate/severe chronic GVHD, OS, disease-free survival (DFS), grade 3–4 acute or extensive chronic GVHD-free/relapse-free survival (GRFS), and relapse and nonrelapse mortality (NRM). All patients were transplanted at the Hematology Clinic of Nantes University Hospital between February 2018 and October 2021 using mobilized PB stem cells as source of graft. All received G-CSF after transplant until PMN recovery. All patients provided informed consent and the study was registered at the French Commission Nationale de l'Informatique et des Libertés as CNIL 2016–038 and approved by the Ethic Review Board of Nantes University Hospital.

M-MDSC were defined by the minimal $CD14^+/CD11b^+/CD33^+/HLA\text{-}DR^{-/low}$ immunophenotypic pattern as reported elsewhere [9]. Cells were assessed in a lysis-no-wash flow cytometry technique using PB collected on EDTA before conditioning then at day +60 (D60) and day +90 (D90) posttransplant. Data acquisition was performed immediately on a Navios® flow cytometer (Beckman Coulter, Miami, FL). Analyses used the Kaluza® software (Beckman Coulter) with a dedicated protocol applied to all samples. M-MDSC were expressed as a percentage (%) of total nucleated cells defined as $CD45^+$.

Statistical analyses were conducted using R software version 4.2.2. Median follow-up was estimated using the reverse Kaplan–Meier method. Patient characteristics were compared using the Chi^2 test for discrete variables and the Mann–Whitney test for continuous variables. OS, DFS, and GRFS were compared using the log-rank test and Kaplan–Meier graphical representation. NRM and relapse were calculated using cumulative incidence and analyzed as competing events. Univariate and multivariate analyses were performed using the Cox proportional-hazard model. Univariate analyses were performed successively considering the whole cohort, patients in complete remission (CR) at transplant and finally only AML patients. Factors considered for univariate analysis were gender, age ($\leq$ or $>$ median), disease (AML vs. ALL), disease-risk index (low/intermediate vs. high/very-high), conditioning (myeloablative [MAC] vs. reduced intensity [RIC] conditioning vs. sequential or RIC vs. MAC for patients in CR at transplant), and M-MDSC% ($\leq$ or $>$ 1.4%). Measurable residual disease (MRD) was also taken into account (positive vs. negative) for patients in CR at transplant and ELN2017 classification (unfavorable vs. others) for AML patients. MRD was evaluated by flow cytometry (negative if $< 10^{-3}$) or RQ-PCR in *NPM1*-mutated cases for AML patients and by a standard molecular method (IG-TCR, negative if $< 10^{-4}$) for ALL. Factors with a p value < 0.10 by univariate analysis, or of interest for the study, were included in multivariate analysis. A p value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Outcomes

Among 73 AML and 14 ALL patients included at diagnosis in the global study [9], 47 and 9 (B-Philadelphia negative $n = 6$, B-Philadelphia

TABLE 1 Patient characteristics.

Characteristic	Whole cohort	Pregraft M-MDSC ≤ 1.4%	Pregraft M-MDSC > 1.4%	*p* Value[a]
Patients *n*	**56**	**35**	**11**	
Gender M/F	35/21 (62%/38%)	21/14 (60%/40%)	5/6 (45%/55%)	0.5
Age median (range) years	51 (20–74)	50 (21–74)	53 (33–69)	>0.9
Disease AML/ALL	47/9 (84%—16%)	29/6 (83%—17%)	9/2 (82%—18%)	>0.9
ELN 2017 risk for AML				
Favorable/intermediate/unfavorable	1/20/26 (2%/43%/55%)	1/12/16 (3%/41%/55%)	0/4/5 (0%/44%/56%)	>0.9
Status at transplant				
CR	44 (79%)	28 (80%)	8 (73%)	>0.9
MRD pos/neg/unknown	21/8/5 (38%/32%/9%)	12/15/1 (34%/43%/3%)	5/1/2 (45%/9%/18%)	
Not CR	12 (21%)	7 (20%)	3 (27%)	
Disease risk index				>0.9
Low/intermediate	1/27 (2%/48%)	1/17 (2.9%/49%)	0/5 (0%/45%)	
High/very high	19/9 (34%/16%)	12/5 (34%/14%)	4/2 (36%/18%)	
Conditioning regimen				
RIC/MAC/Sequential	36/9/11 (64%/16%/20%)	22/7/6 (63%/20%/17%)	7/1/3 (64%/9%/27%)	
Donor type				
MDS/MUD/haploidentical	17/11/26 (20%/30%/46%)	6/12/17 (17%/34%/49%)	2/2/6 (18%/18%/55%)	
MMUD/cord blood	1/1 (2%/2%)	0/0 (0%/0%)	1/0 (9%/0%)	

Abbreviations: ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CR, complete remission; fav, favorable; inter, intermediate; M-MDSC, monocytic-myeloid-derived suppressive cells; MAC, myeloablative conditioning; MMUD, mismatched unrelated donor; MRD, measurable residual disease evaluated by flow cytometry for AML and by molecular biology (IG-TCR) for ALL; MSD, matched sibling donor; MUD, matched unrelated donor; Ph, Philadelphia; RIC, reduced-intensity conditioning.

[a]Fisher exact test; Wilcoxon rank-sum test.

positive $n = 1$, T-ALL $n = 2$), respectively, were ultimately allografted and considered for this report. Patient characteristics are provided in Table 1. All 56 patients engrafted. The median follow-up was 35.8 months (interquartile range [IQR]: 25.4–47.3). Three-year OS, DFS, and GRFS were, respectively, 61% (95%CI: −49 to 76%), 59% (95%CI: 47–73%), and 34% (95%CI: 23–49%), while 3-year NRM and relapse incidence were 11% (95%CI: 4.3–20%) and 31% (19–43%). Grade 2–4 and 3–4 acute GVHD occurred in 16 and 11 patients, at medians of 30 days (range: 20–123) and 30 days (range: 22–123) posttransplant, respectively. The 3-year incidence of moderate/severe chronic GVHD was 21% (95%CI, 12%–33%). OS, DFS, and NRM were not significantly different between AML and ALL patients, neither was the 3-year incidence of relapse (30% vs. 33%, $p = 0.8$).

3.2 | Impact of pregraft peripheral level of M-MDSC

Samples could not be collected for 10 patients; hence 46 patients out of 56 were evaluated at a median of 20 days before Day 0 of Allo-HSCT (range: 6–83). The median pregraft % of M-MDSC was 0.45% (range: 0–11.85) with no differences between AML and ALL patients ($p = 0.32$). The best cut-off for prediction of relapse, assessed by ROC curve analysis, was 1.4%. Of note, patients with pregraft peripheral M-MDSC ≤ or > 1.4% shared not significantly different characteristics (Table 1).

In univariate analysis, according to this threshold, no impact on GRFS (Figure 1A), NRM (Figure 1B), or acute and chronic GVHD was observed. Conversely, in patients with > 1.4% of M-MDSC, OS (Figure 1C), and DFS (Figure 1D) were significantly lower at 3 years: 36% (95%CI: 17%, 79%) vs. 68% (95%CI: 55%, 86%), $p = 0.04$ and 27% (95%CI: 10%, 72%) vs. 66% (95%CI: 52%, 83%), $p = 0.03$, respectively. The incidence of cytologic relapse at 3 years was significantly higher, at 73% (95%CI: 32–91%) vs. 17% (95%CI: 6.9–32%), $p < 0.001$ (Figure 1E).

In multivariate analysis, to assess the risk of relapse, the pregraft M-MDSC percentage together with the disease risk index (DRI; low/intermediate versus high/very high, HR: 2.19 [95%CI: 0.76–6.30], $p = 0.150$, in univariate analysis but considered as the most relevant variable) were taken into account. A higher pregraft M-MDSC percentage remained the only factor associated with a higher risk of relapse (HR: 5.94 [95%CI: 2.09–16.87], $p = 0.001$). No factor was associated with OS or DFS.

Considering the group of patients who were in CR prior to transplant ($n = 44$), a higher pregraft M-MDSC percentage (>1.4%) remained associated to a higher 3-year incidence of relapse (75% vs. 11%, $p < 0.001$). In multivariate analysis, considering the DRI and negative MRD prior to transplant as competitive variables, high M-MDSC

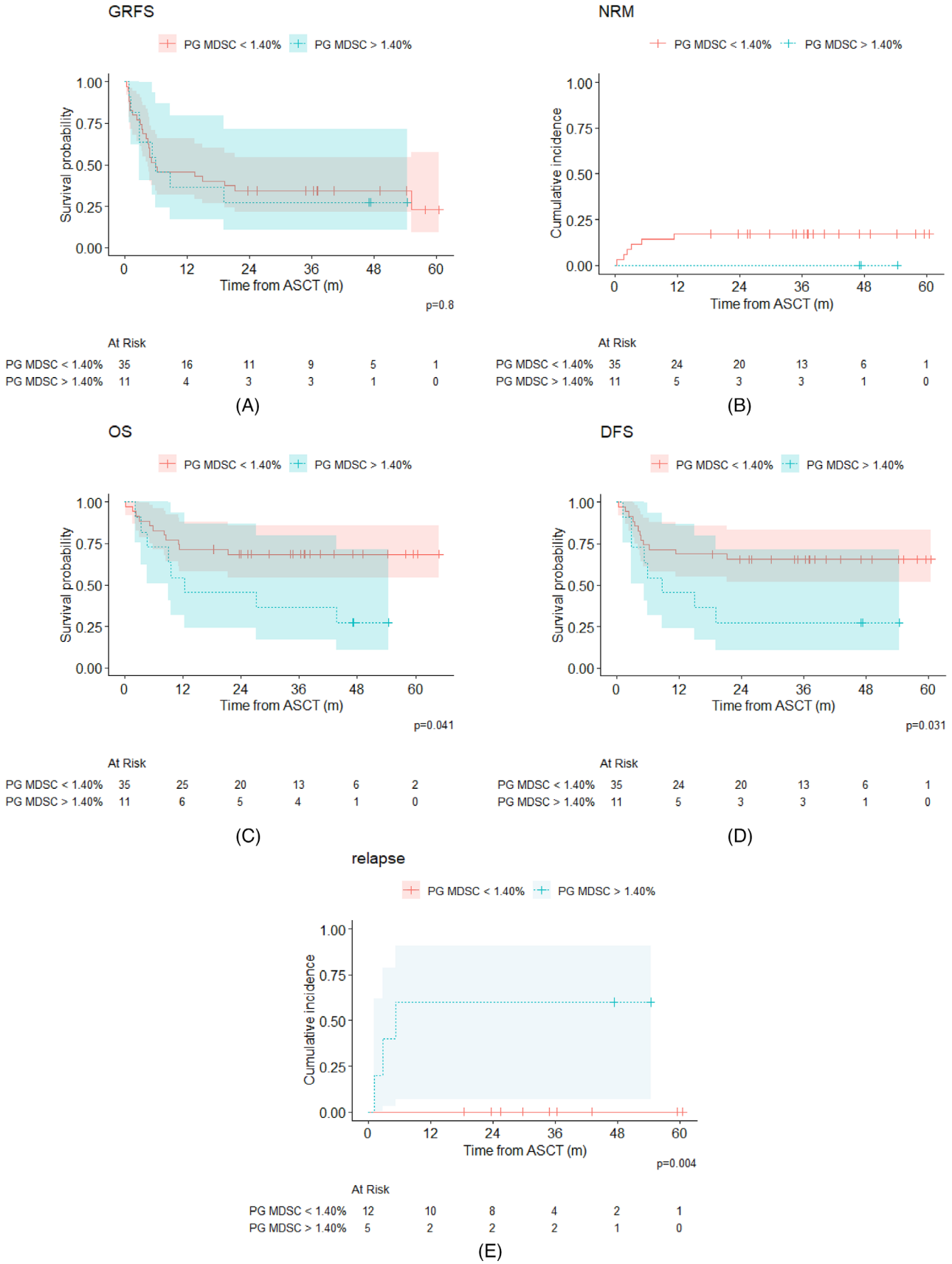

FIGURE 1 Whole cohort, comparison of patients with M-MDSC ≤ or > 1.4% before conditioning. (A) Overall survival (OS), (B) GVHD-free relapse-free survival (GRFS); (C) nonrelapse mortality (NRM); (D) disease-free survival (DFS); (E) incidence of relapse in patients with M-MDSC ≤ or > 1.4% before conditioning.

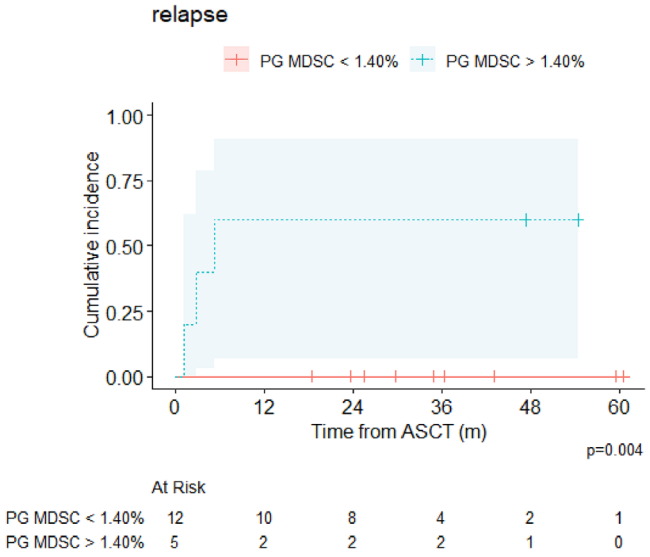

FIGURE 2 Incidence of relapse in patients with negative MRD at transplant according to pretransplant M-MDSC% (≤ or > 1.4%).

percentages remained associated with relapse (HR: 55.01 [95%CI: 14.95–202.37], $p < 0.001$), together with a pregraft-positive MRD (HR: 11.04 [95%CI: 1.89–64.67], $p = 0.008$). A higher pregraft M-MDSC percentage was also associated with a lower OS and DFS in multivariate analysis (HR: 6.05 [95%CI: 1.24–29.59], $p = 0.026$ and HR: 6.52 [95%CI: 1.41–30.19], $p = 0.016$, respectively). This was not the case for pregraft MRD (HR: 3.01 [95%CI: 0.72–12.57], $p = 0.131$). Very remarkably, in patients with a negative MRD, no relapse occurred in those with a M-MDSC level ≤1.4%, vs. a 3-year relapse incidence of 60% (6.7%—91%) for those with M-MDSC% > 1.4% ($p = 0.004$; Figure 2) while OS ($p = 0.10$) and DFS ($p = 0.08$) were not significantly different. Of note, no association existed between pregraft MDSC and MRD status.

Finally, considering only AML patients ($n = 47$), higher M-MDSC levels were associated with a higher risk of relapse, confirmed in multivariate analysis (HR: 4.30 [95%CI: 1.20–15.48], $p = 0.025$; Figure 3A), while there was a nonsignificant trend for lower DFS (3-year DFS: 33% vs. 65%, $p = 0.10$; Figure 3B).

3.3 | Impact of postgraft peripheral levels of M-MDSC

Forty-two patients were evaluated at a median of 61.5 days after Day 0 of Allo-HSCT (D60, range: 40–77). At this time point, the median postgraft percentage of M-MDSC was 0.52% (range: 0–5.03) with no differences between AML and ALL patients ($p = 0.32$). Thirty-six patients were evaluated at a median of 92 days (D90, range: 89–132). At this time point, the median postgraft percentage of M-MDSC was 0.3% (range: 0–2.95), again without difference between AML and ALL patients ($p = 0.29$).

No best cut-off for relapse was determined by ROC analyses at D60 or D90. Survivals were not significantly different between patients with equal/less or more than the median values of M-MDSC (0.52% D60 and 0.3% at D90). No significantly difference incidence of relapse, NRM, or chronic GVHD was observed either at both time points. As postgraft M-MDSC percentages were evaluated after the occurrence of acute grade 2–4 and 3–4 GVHD, and thus could not be taken into account as a predictive factor, median M-MDSC levels were compared between patients who had presented an acute GVHD or not, at D60 and D90. Interestingly, patients who had presented grade 2–4 acute GVHD were found to have statistically significantly higher median M-MDSC percentages at D90 compared to others (1.1% [0.26–2.95] vs. 0.23% [0–2.78], $p = 0.003$). Similarly, patients with grade 3–4 acute GVHD had significantly higher median levels of M-MDSC, both at D60 (1.36% [0–3.6] vs. 0.38% [0–5.03], $p = 0.04$) and D90 (1.24% [0.26–2.95] vs. 0.29% [0–2.78], $p = 0.007$).

3.4 | Impact of peripheral levels of M-MDSC kinetics

The increase or decrease of peripheral M-MDSC levels between before Allo-HSCT and at D60 or D90 had no influence on outcomes.

4 | DISCUSSION

Here, peripheral levels of M-MDSC were prospectively evaluated pre- and post-Allo-HSCT (D60 and D90) in adult AML or ALL patients. The objective was to appreciate the potential influence of these cells levels not only on the incidence of GVHD and outcomes, but also on the GVL effect, a relationship that has been poorly studied so far in humans [15]. Higher pregraft percentages of M-MDSC (> 1.4% of total nucleated cells) were found to be associated with a higher risk of relapse and lower DFS in patients in CR at transplant, by multivariate analysis. In addition, patients having developed grade 2–4 or grade 3–4 acute GVHD at a median of 30 days post-Allo-HSCT, showed thereafter (D60 and/or D90) higher M-MDSC levels compared to other patients.

An important outcome of this study is the correlation between higher levels of peripheral M-MDSC before Allo-HSCT, risk of relapse, DFS and OS. Indeed, this correlation has been only reported so far in two studies, yet considering M-MDSC levels early after transplant (within the first 30 days) [12, 13]. Here, PB was sampled on D60 and D90 when M-MDSC levels were no longer predictive of relapse. Globally, these data confirm the negative impact of higher levels of M-MDSC both at diagnosis (published part 1 of this work) [9] and before transplant in acute leukemia, at least in AML. If the mechanisms by which MDSC may protect leukemic cells (including residual cells) have not been fully explored in the setting of Allo-HSCT, a role for the matrix metalloproteinase-9 (MMP-9) has been suggested in one of the above-mentioned studies [12]. Indeed, it was shown that M-MDSC produce abundant amounts of MMP-9 post-HSCT and had a greater capacity to suppress T cell responses. Moreover, MMP-9 blockade forcefully inhibited their immunosuppressive effect [12]. The second study [13]

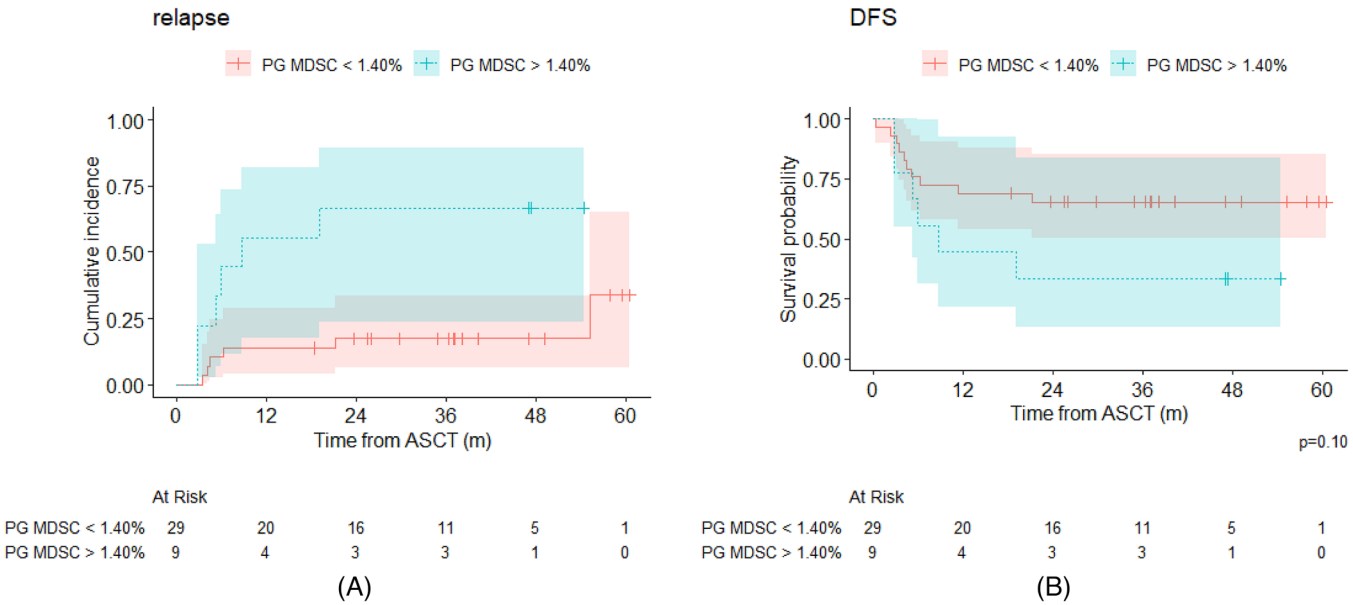

FIGURE 3 AML cohort. (A) Relapse incidence and (B) disease-free survival (DFS), between patients with M-MDSC < or > 1.4% before conditioning.

suggests a role for immature NKT cells, the potency of these cells after Allo-HSCT being likely inhibited by the expansion of M-MDSCs (better GVL effect if more iNKT cells and less M-MDSCs).

Interestingly, it was possible here to compare the impact of both pregraft MRD and M-MDSC levels in patients in CR at the time of transplant. MRD is a well-known predictive factor of survival and/or relapse in both AML [16, 17] and ALL [17, 18]. Here, these factors were independently associated with relapse. However, only M-MDSC levels correlated with DFS. Therefore, the assessment of M-MDSC levels may improve the ability to predict posttransplant outcomes. Moreover, as relapse still occurs in a minority of MRD-negative patients, the significant association between M-MDSC percentage and relapse in this context provides an opportunity to closely monitor individuals with high levels of pretransplant M-MDSCs and to propose early posttransplant intervention(s). However, these findings need to be validated on larger cohorts.

Also of note, it is shown here that patients developing grade 2–4 or 3–4 acute GVHD had higher levels of postgraft peripheral M-MDSCs at D60 and D90. This seems paradoxical as the protective role of MDSC against GVHD has been largely reported in the literature [10–15]. This protection is thought to be linked to the inhibition of alloreactive T cells via various mechanisms, such as NO production, arginase 1-mediated L-arginine depletion, indoleamine 2,3-dioxygenase (IDO)-mediated tryptophan conversion, and Treg induction [15]. No predictive value can be drawn from our data since the median time of severe GVHD occurrence was 30 days posttransplant, and thus before M-MDSC evaluation. However, a possible interpretation could be that an amplification of immunosuppressive M-MDSCs occurs as a reaction to GVHD. Of note, dynamic changes and an increase of M-MDSCs after GVHD have already been reported by Yin et al. [19] and Mugiakos et al. [20], while this was not observed by others [12, 21].

Finally, the findings reported here suggest that targeting pregraft peripheral M-MDSC could be a good strategy to prevent tumor progression after Allo-HSCT. Various MDSC-inhibiting strategies are being considered, including a direct attack of MDSC applying such agents as tyrosine kinase, IL-6R or S100A9 inhibitors, metformin, or anti-CD38 monoclonal antibodies. Other strategies aim to induce MDSC differentiation into mature myeloid cells through the use, for example, of vitamins A, D3 or E or ATRA, or to promote MDSC deactivation via the down regulation of arginase-1 or NOS2 expression, these molecules being highly expressed by activated MDSC [4, 6].

In conclusion, this prospective study demonstrates a negative impact of higher proportions of peripheral M-MDSC before allotransplant in leukemic patients. This paves the way to therapeutic intervention to decrease M-MDSC before transplant and thus perhaps the incidence of relapse in such patients.

AUTHOR CONTRIBUTIONS

PP, MCB, and PC designed, performed, coordinated the research, analyzed, interpreted the data, and wrote the manuscript. CD and ME coordinated immunophenotyping schedules, performed immunophenotypic analysis, generated the data, and commented on the manuscript. MCB performed immunophenotypic analysis and helped writing the manuscript. MJ performed statistical analyses, generated the data and figures, and helped writing the manuscript. AG, ALB, TG, ME, and MJ recruited patients, provided data, and commented on the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

FUNDING INFORMATION

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ETHICS STATEMENT

The study was approved by the Ethic Review Board of Nantes University Hospital.

PATIENT CONSENT STATEMENT

All patients provided informed consent.

CLINICAL TRIAL REGISTRATION (INCLUDING TRIAL NUMBER)

The study was registered at the French Commission Nationale de l'Informatique et des Libertés as CNIL 2016–038

DATA AVAILABILITY STATEMENT

The datasets generated during the current study are available from the corresponding author on reasonable request.

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