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RESEARCH LETTER

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Delayed persistence of elevated monocytic MDSC associates with deleterious outcomes in septic shock: a retrospective cohort study

Louis Waeckel¹, Fabienne Venet^{1,2}, Morgane Gossez^{1,2}, Céline Monard^{2,3}, Thomas Rimmelé^{2,3} and Guillaume Monneret^{1,2*}

Keywords: MDSC, Sepsis, HLA-DR, Monocyte, Flow cytometry

To the editor,

Recent observations indicate that some septic patients, after inaugural inflammation, enter a stage of protracted immunosuppression that may take weeks/months to vanish and associate with increased rate of secondary infections and mortality [1]. Delayed elevation of myeloid-derived suppressor cells (MDSC) has recently been hypothesized as a key mechanism sustaining sepsis-induced immunosuppression [2, 3]. These cells constitute a heterogeneous population of immature myeloid cells characterized by their capacity to suppress T cell response [4]. There are 3 major MDSC subsets [5]: granulocytic/neutrophilic MDSC (PMN-MDSC phenotypically and morphologically similar to neutrophils), monocytic MDSC (M-MDSC phenotypically and morphologically similar to monocytes), and early MDSC (eMDSC) which are largely immature and do not express any lineage markers. In humans, M-MDSC are mainly defined as CD14+HLA-DR^{low} monocytes [5]. In various cancers, these cells revealed as valuable predictive markers of pejorative evolution and as potential

targets for innovative therapeutic interventions aimed at abrogating their deleterious immunosuppressive properties. Interestingly, our lab has been focusing for years on the monitoring of the decreased expression of HLA-DR on monocytes (mHLA-DR) in septic shock patients (IMMUNOSEPSIS cohort, #NCT02803346) according to a flow cytometry protocol combining CD14 and HLA-DR detections. Results are expressed as numbers of anti-HLA-DR antibodies bound per monocyte (AB/C) [6]. This parameter has been reported as a reliable predictor of deleterious outcomes after sepsis [1].

According to recommendations for M-MDSC characterization, we developed an automated standardized reanalysis protocol (Altrabio algorithm, www.altrabio.com) to investigate our results under a “MDSC” angle (Fig. 1a). The objective was to assess whether, as in cancer, %M-MDSC may provide relevant clinical information. This percentage was recalculated in 301 patients with septic shock (similar to the recent Sepsis-3 criteria). These patients were enrolled from March 2014 to July 2018 and sampled at days 1–2 and/or days 3–4 and days 6–8 (if still present in ICU) after syndrome onset. Mortality, assessed at day 28, was 34%. Fifty patients (15%) developed ICU-acquired infection (HAI). At days 3–4, these patients presented with usual features of sepsis-induced immunosuppression, i.e., very low mHLA-DR (AB/C), 5150 [3115–8250], and severe lymphopenia: CD4 lymphocyte/ μ L, 362 [245–591].

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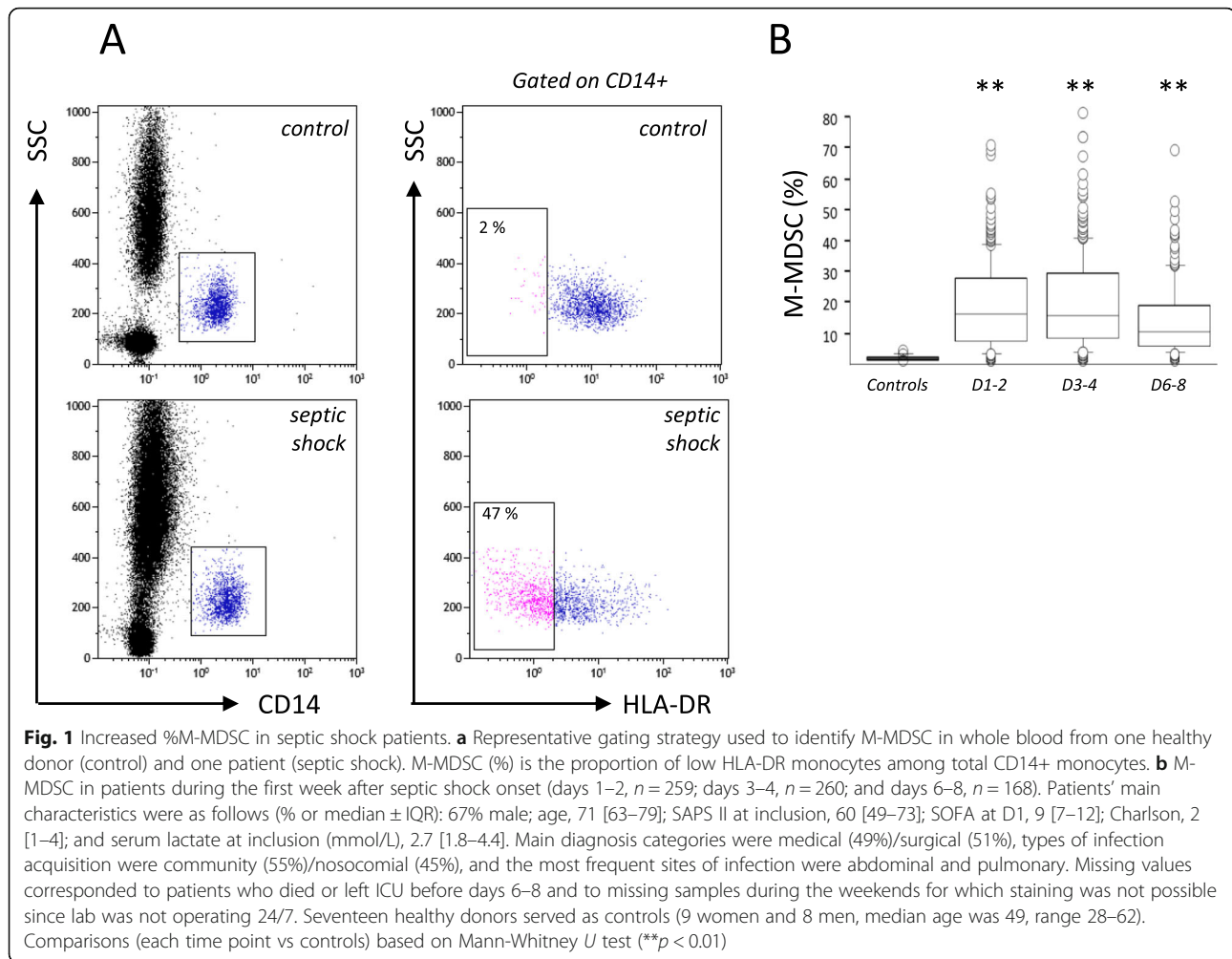
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We observed a marked elevation of M-MDSC in patients in comparison with healthy controls ($n = 18$, all values $< 2\%$, Fig. 1b). Not surprisingly, there was a strong negative correlation between mHLA-DR and %M-MDSC. Regarding M-MDSC association with deleterious outcomes (i.e., 28-day mortality or HAI), we did not find any difference at the first time points. However, at days 6–8, patients who were going to die or to get infected presented with significantly higher M-MDSC values (Fig. 2a, b). These associations remained significant in multivariate analyses including usual potential confounders (age, gender, SAPS II, SOFA, comorbidities, mechanical ventilation). Calculated odds ratios were 4.4 ($p = 0.001$) and 2.4 ($p = 0.013$) for mortality and nosocomial infection occurrence, respectively. Accordingly, Kaplan-Meier representations clearly illustrate the pejorative evolution of patients with the highest M-MDSC values (Fig. 2a, b).

Due to its retrospective nature, the current report presents with limitations. Indeed, while our findings strongly suggest that CD14+HLA-DR^{low} cells are M-

MDSC, definitive proof of their M-MDSC phenotype is presently lacking (i.e., CD15 staining and functional testing). Awaiting confirmation, they may be called “M-MDSC-like cells.”

Overall, the present results provide robust complementary information to that recently published by Hollen and colleagues [3]. Indeed, we observed that the persistence of increased M-MDSC after 1 week was significantly associated with worsening.

Abbreviations

HLA-DR: Human leukocyte antigen—DR isotype; MDSC: Myeloid-derived suppressor cells; AB/C: Antibodies bound per monocyte; ICU: Intensive care unit

Acknowledgements

Not applicable.

Authors' contributions

LW, MG, FV, and GM designed and performed the experiments. LW performed the statistical analyses. TR and CM included patients. All authors discussed the data, drafted or revised critically the manuscript for important intellectual content, and approved the final manuscript.

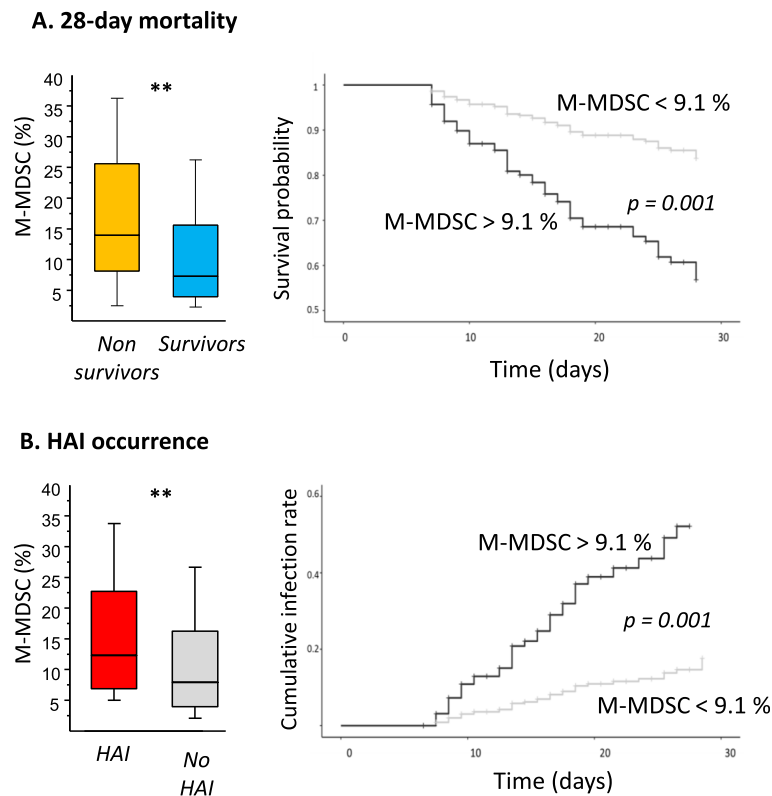


Fig. 2 %M-MDSC at days 6–8 associated with clinical outcomes. **a** %M-MDSC among total monocyte population at days 6–8 after septic shock according to survival status at day 28: survivors ($n = 123$) and non-survivors ($n = 45$). Left, comparison between groups: Mann-Whitney (** $p < 0.01$). Right, Kaplan-Meier survival curves, patients were stratified in 2 groups based on median %M-MDSC value at days 6–8, difference between curves based on log-rank test. **b** %M-MDSC among total monocyte population at days 6–8 after septic shock according to the occurrence of health care-associated infections (HAI): patients developing HAI ($n = 39$) or not ($n = 129$). Left, comparison between groups: Mann-Whitney (** $p < 0.01$). Right, cumulative incidence curves for HAI stratified based on median %M-MDSC value at days 6–8, difference between curves based on log-rank test

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This project was approved by our Institutional Review Board for ethics ("Comité de Protection des Personnes Sud-Est II", number 11236). This study is registered at the French Ministry of Research and Teaching (#DC-2008-509), at the Commission Nationale de l'Informatique et des Libertés, and on clinicaltrials.gov (NCT02803346). Oral information and non-opposition to inclusion in the study were mandatory and recorded in patients' clinical files. Peripheral blood from healthy volunteers was provided by the "Etablissement Français du Sang" from Lyon. According to EFS standardized procedures for blood donation and to provisions of the articles R.1243–49 and following ones of the French public health code, a written non-opposition to the use of donated blood for research purposes was obtained from HV. The blood donors' personal data were anonymized before transfer to our research laboratory.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no conflict of interest.

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