# High pre-transplant Mucosal Associated Invariant T Cell (MAIT) count predicts favorable course of myeloid aplasia

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**Aims.** Mucosal Associated Invariant T (MAIT) cells are unconventional T cells with anti-infective potential. MAIT cells detect and fight against microbes on mucosal surfaces and in peripheral tissues. Previous works suggested that MAIT cells survive exposure to cytotoxic drugs in these locations. We sought to determine if they maintain their anti-infective functions after myeloablative chemotherapy.
**Methods.** We correlated the amount of MAIT cells (measured by flow cytometry) in the peripheral blood of 100 adult patients before the start of myeloablative conditioning plus autologous stem cell transplantation with the clinical and laboratory outcomes of aplasia.
**Results.** The amount of MAIT cells negatively correlated with peak C-reactive protein level and the amount of red blood cell transfusion units resulting in earlier discharge of patients with the highest amount of MAIT cells.
**Conclusion.** This work suggests the anti-infectious potential of MAIT cells is maintained during myeloid aplasia.

**Key words:** MAIT cells, ASCT, infection, complications

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## INTRODUCTION

Mucosal-associated invariant T (MAIT) cells are a recently discovered population of T cells. MAIT cells are often called unconventional, as they differ in many ways from classical major histocompatibility complex (MHC) restricted T cells[1-3]. Unlike highly polymorphic classical MHC molecules that present peptides, MAIT cells recognize metabolites of vitamin B presented by monomorphic MHC class I-like protein (MR1) (ref.[4,5]). Contrary to the infinite repertoire of conventional MHC restricted T cells, MAIT cells' repertoire is conserved, consisting of an invariant T cell receptor (TCR) α-chain (Vα7.2-Jα33) associated with limited TCR β-chain repertoire[6,7]. MAIT cells can be detected in human blood, where they account for approximately 5% of T cells[8] , and they are enriched on mucosal surfaces and in the liver, where they account for up to 35% of T cells[5]. The main function of MAIT cells is probably to protect the mucosal barriers against invading microbes. Indeed, MAIT cells respond to a broad range of microbial organisms including Staphylococcus aureus, E. coli, Mycobacterium tuberculosis or Candida albicans[9,10]. Grimaldi and colleagues provided clinical proof of the concept of antimicrobial surveillance by MAIT cells. The prospective study on intensive care unit (ICU) showed that patient with MAIT cell depletion had a higher incidence of ICU-acquired infections[11].

Our recent study suggested that MAIT cells kept their anti-infective potential even after myeloablative conditioning and autologous stem cell transplantation (ASCT). The pilot study on 29 patients showed that patients with the highest amount of MAIT cells pre-transplant tended to have less infectious complications during aplasia as measured by peak C-reactive protein (CRP) level, febrile days or days on intravenous antibiotics[12]. Here we report results of extended blind prospective study on 100 patients designed to confirm or disprove the hypothesis of anti-infective potential in MAIT cells during myeloid aplasia.

## MATERIALS AND METHODS

### Patients

The studied population consisted of 100 patients treated by high-dose chemotherapy and autologous stem cell transplantation in the Department of Haematology of the 3rd Faculty of Medicine, Charles University and Faculty Hospital Kralovske Vinohrady, Czech Republic. Further characteristics of the patients are provided in Table 1 and the Results section. The research was carried out in accordance with the latest Declaration of Helsinki and was approved by the local ethics committee (Ethics committee of the 3rd Faculty of Medicine, Charles University, Czech Republic, dated 16 Nov 2016).

**Table 1.** Clinical characterization of the patients.

| | | |
|---|---|---|
| Patients | | 100 |
| Gender (M/F) | | 58/42 |
| Median (range) age (years) | | 61 (25–73) |
| Primary diagnosis | R/R HL | 9 |
| | R/R NHL | 22 |
| | First line NHL | 12 |
| | Myeloma | 57 |
| Months from diagnosis to transplant | median (range) | 11.5 (3–313) |
| Number of pretransplant treatments (lines) | | 1.5 (1–6) |
| Clinical outcome pre-ASCT | CR or PR | 94 |
| | SD or PD | 6 |
| The time interval (days) from last chemotherapy | median (range) | 89.5 (12–408) |
| Conditioning regimens | BEAM | 37 |
| | HD Mel | 48 |
| | BuMel | 10 |
| | carmustine/thiotepa/etoposid | 4 |
| | carmustine + thiotepa | 1 |

R/R, relapsed/refractory; HL, Hodgkin lymphoma; NHL, Non-Hodgkin Lymphoma; ASCT, Autologous stem cell transplantation; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; BEAM, BiCNU/carmustine, etoposide, Ara-C, melphalan; HD, High-dose; Mel, melphalan; BiCNU, bis-chloroethylnitrosourea.

**Conditioning regimens**

The following myeloablative regimens were used: BEAM (carmustine 300 mg/m$^2$ on day -6; etoposide 100 mg/m$^2$ twice a day on days -5, -4, -3, and -2; cytarabine 100 mg/m$^2$ twice a day on days -5, -4, -3, and -2; and melphalan 140 mg/m$^2$ on day -1), high-dose melphalan (melphalan 200 mg/m$^2$ on day -1), carmustine, thiotepa and etoposide (carmustine 400 mg/m$^2$ on day -5; thiotepa 5 mg/kg twice a day on days -4 and -3; and etoposide 150 mg/m$^2$ on days -5, -4, and -3), BuMel (busulfan 3 mg/kg on days -6, -5, -4, and -3; melphalan 140 mg/m$^2$ on day -2) and carmustine + thiotepa (carmustine 400 mg/m$^2$ day –6, thiotepa 2×5 mg/kg/day on days -5 and -4). The transplant was performed if at least 3.0×10$^6$/kg CD34+ peripheral blood stem cells were available.

**Supportive treatment**

Supportive care was provided according to institutional guidelines. Anti-infective prophylaxis started the day after peripheral stem cell transfer, in some cases earlier with the early onset of cytopenia. Prophylaxis consisted of antibacterial (ciprofloxacin 500 mg twice a day) antipneumocystis (sulfamethoxazole 400 mg/trimethoprim 80 mg once a day), antifungal (fluconazole 100 mg twice a day) and antiviral (aciclovir 400 mg twice a day or valaciclovir 500 mg twice a day) prophylaxis.

According to the institutional guidelines, the G-CSF support was started on day +8 in lymphoma patients and on day +10 in myeloma patients. In case of severe infectious complications, the G-CSF was started earlier.

**Table 2.** Laboratory characterization of the patients pretransplant.

| | |
|---|---|
| Leukocytes x 10$^9$/mL, median (range) | 4.85 (1.8–10.7) |
| Lymphocytes %, median (range) | 19.1 (1.7–51.6) |
| Lymphocytes x 10$^9$/mL, median (range) | 0.95 (0.13–2.68) |
| T cells % (from lymphocytes), median (range) | 64.65 (25.1–93.26) |
| MAIT cells % (from T cells), median (range) | 0.89 (0.03–11.3) |
| MAIT cells /μL, median (range) | 5.55 (0.13–11.3) |

**Patient monitoring and blood sampling**

Laboratory biochemical and haematological parameters were measured by routine clinical protocols from admission to the discharge of the patient. Blood cells were analysed daily by an automatic Sysmex XN-1000 machine using standard certified procedures. In some patients, the enumeration was confirmed by optical microscopy.

**Flow cytometry**

The MAIT cell count in peripheral blood was measured by flow cytometry before the start of high-dose chemotherapy on the day of admission for transplantation. The samples (whole peripheral blood in EDTA) were

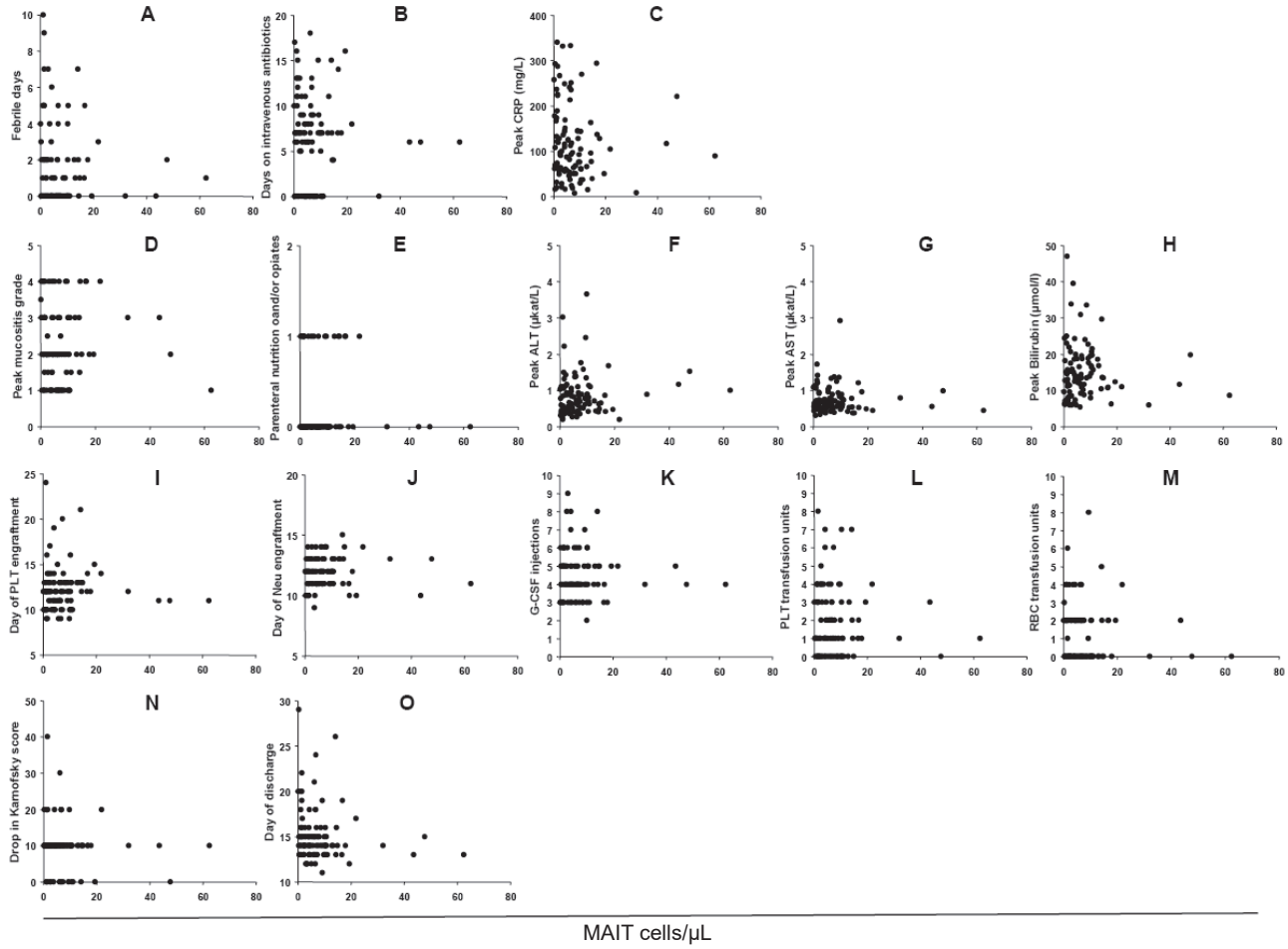


**Fig. 1.** Correlation between the amount of MAIT cells and clinical/laboratory outcomes of myeloid aplasia.
Each dot corresponds to an individual patient and shows a correlation between the amount of MAIT cells/µL measured a day before the start of myeloablative conditioning and: **A.** Febrile (≥ 38 °C) days. **B.** Days on intravenous antibiotics. **C.** Peak CRP (C-reactive protein) level during aplasia. **D.** Peak mucositis grade. **E.** Requirement of parenteral nutrition (Yes/No). **F.** Peak ALT (alanine aminotransferase) level during aplasia. **G.** Peak AST (aspartate aminotransferase) level during aplasia. **H.** Peak bilirubin level during aplasia. **I.** Day of platelet engraftment. J. Day of neutrophile engraftment. **K.** Amount of G-CSF (Granulocyte Colony Stimulating Factor) injections. **L.** Amount of red blood cell transfusion units (RBC). **M.** Amount of platelet transfusion units. **N.** Drop in Karnofsky score. **O.** Day of discharge.

stained, washed (PBS), and lysed by $NH_4Cl$. MAIT cells were defined as follows: CD3 PerCP-Cy5.5 (UCHT1) positive, TCR γ/δ PE-Cy7 (11F2) negative, TCR Vα7.2 APC (3C10) positive and CD161 APC-Cy7 (HP-3G10) bright. Monoclonal antibodies were purchased from BD Pharmingen and Biolegend. Cells were acquired with a FACSCantoII (BD Biosciences). Flow cytometry data was analysed by the software application FlowJo (Tree Star).

**Engraftment**

Granulocyte engraftment was defined as the first of 3 consecutive days with an ANC (Absolute Neutrophil Count) over $0.5\times10^9$/L. Platelet engraftment was defined as the first of three consecutive days with platelet count over $20\times10^9$/L without the need for platelet transfusion.

**Clinical parameters**

Clinical data and laboratory biochemical markers were analysed retrospectively and independently from data on MAIT cells. Mucositis was scored according to the NCI-CTCAE Grading Scale classification. All clinical parameters (febrile days, days of intravenous antibiotic application, days on opioid analgesics and parenteral nutrition, grade of mucositis, Karnofsky score) were monitored daily.

**Statistical analysis**

The data were analysed using non-parametric (Spearman's Rho) and parametric (Pearson's Rho) correlation coefficient. In the case of Pearson's correlation, we had to normalize the data. The results of the two tests were comparable. We tested the independence for each pair of variables using the t-test. Correlation coefficient Rho shows the power of statistical dependence between the pair of considered variables. A positive coefficient indicates possible agreement and a negative coefficient value indicates possible disagreement.

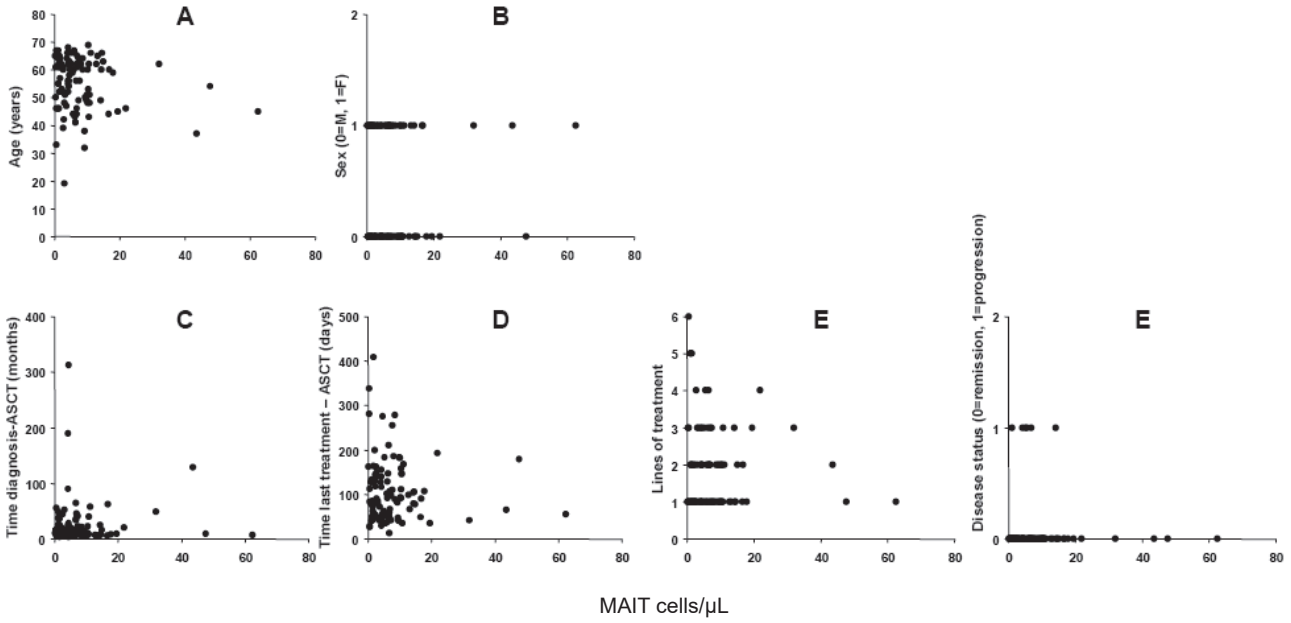


**Fig. 2.** What factors influence the amount of MAIT cells pretransplant?
Each dot corresponds to an individual patient and shows a correlation between an amount of MAIT cells/µL measured a day before start of myeloablative conditioning and: **A.** Age. **B.** Sex. **C.** Time between the diagnosis of the malignancy and ASCT (Autologous Stem Cell Transplantation). **D.** Time between the last treatment and ASCT. **E.** Lines of previous treatments. **F.** Disease status at ASCT (remission Yes/No).

## RESULTS

### 1. Clinical characteristics of the patients

100 patients treated for Hodgkin lymphoma, non-Hodgkin lymphoma and Plasma cell myeloma indicated for myeloablative conditioning and autologous stem cell transplantation were recruited (Table 1). The median age was 61 (range 25–73). The vast majority of the patients were in remission before the start of conditioning (94 patients). According to the underlying disease, the conditioning consisted of either BEAM (carmustine, etoposide, cytarabine and melphalan; 37 patients) or high-dose melphalan (HD-Mel; 48 patients), busulphan and melphalan (BuMel; 10 patients), carmustine, thiotepa and etoposide (4 patients) or carmustine + thiotepa (1 patient). All patients underwent several lines of cytotoxic treatments (median 1.5, range 1–6) before myeloablative conditioning. The mean time from the last treatment to ASCT varied from 12 days to 408 days (with a median of 89.5).

### 2. Immunological laboratory description of the patients

The median lymphocyte count and percentage of lymphocytes among white blood cells was on the lower limit of the normal (Table 2). The median percentage of MAIT cells among T cells was 0.89% and the median amount of MAIT cells per microliter was 5.55. These values are lower than in the general population of corresponding age, reflecting the exposure to previous cytotoxic treatments and possibly interaction with cancer cells[13,14].

### 3. Correlation of pretransplant MAIT cell count with clinical complications of myeloid posttransplant aplasia

Myeloablative conditioning induces deep thrombocytopenia and neutropenia leading to the risk of bleeding, infections and injury of the mucosal surface. We hypothesized that MAIT cells survived the myeloablative conditioning and maintained their function. We thus investigated the correlation between pretransplant MAIT cell count and clinical and laboratory markers of early posttransplant complications. Regarding infectious complications, we failed to find a significant correlation between MAIT cell count and febrile days (Fig. 1A, Spearman's Rho=-0.123, $P$=0.111) or days on intravenous antibiotics (Fig. 1B, Spearman's Rho=-0.142, $P$=0.080). MAIT cell count showed a significant negative correlation with peak C-reactive protein levels (CRP); (Fig. 1C, Spearman's Rho=-0.176, $P$=0.040).

Mucositis is inflammation of the oral mucosa induced by chemotherapy and bone marrow transplantation. It is associated with leukopenia and possibly with bacterial colonization. It was thus reasonable to correlate MAIT cell count with the severity of mucositis[15].

We failed to reveal any correlation between MAIT cell count and the peak WHO grade of mucositis (Fig. 1D, Spearman's Rho=-0.056, $P$=0.288) or MAIT cell count and the use of parenteral nutrition (Student's t-test $P$=0.313) or intravenous opioids (Student's t-test $P$=0.966), (Fig. 1E).

Both anatomical (mucositis) and functional (cytopenia) disruption of the antimicrobial barrier may lead to liver injury, as the liver is crucial for clearing toxins

and pathogens that reach the circulatory system from the gut. Better control of microbes in the gut by MAIT cells may result in milder liver injury[16]; we thus measured bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. The peak level from a period of aplasia was correlated with the pretransplant MAIT cell count. None of the parameters showed any correlation with pretransplant MAIT cell count (ALT; Fig. 1F, Spearman's Rho=0.149, *P*=0.069), (AST; Fig. 1G, Spearman's Rho=0.017, *P*=0.431), (bilirubin; Fig. 1H, Spearman's Rho=0.041, *P*=0.342).

The clinical characteristics usually used to describe the course of aplasia also involve the day of neutrophile and platelet engraftment (for definition see material and methods), the amount of platelet transfusion units used and the use of granulocyte colony stimulating factor (G-CSF) injections. There was no correlation between pretransplant MAIT cell count and the day of platelet engraftment (Fig. 1I, Spearman's Rho=0.131, *P*=0.096), the day of neutrophile engraftment (Fig. 1J, Spearman's Rho=0.105, *P*=0.149), the number of G-CSF injections (Fig. 1K, Spearman's Rho=-0.089, *P*=0.190) or the amount of platelet transfusion units (Fig. 1L, Spearman's Rho=-0.093, *P*=0.178). Significantly negative correlation was found between MAIT cell count and red blood cell transfusion units (Fig 1M, Spearman's Rho=-0.180, *P*=0.036).

All mentioned parameters merge into two key clinical parameters: day of discharge and drop in Karnofsky score. While there was no a significant correlation between drop in Karnofsky score (Fig. 1N, Spearman's Rho=-0.116, *P*=0.125), we found a significant negative correlation between pretransplant MAIT cell count and the day of discharge (Fig. 1O, Spearman's Rho=-0.175, *P*=0.041). Patients with a high amount of MAIT cells pretransplant were likely to be discharged earlier. Owing to the heterogeneity of the patients, we conducted separate analysis of two homogenous groups of patients. The first group contained only multiple myeloma patients treated with Mel200 (Supplemetary Fig. 1). The other group contained only NHL patients treated with BEAM (Supplemetary Fig. 2). MAIT cell amount negatively correlated with a day of discharge in both groups. Moreover, the amount of MAIT cells negatively correlated with febrile days and amount of transfusion units of both red blood cells and platelets within the BEAM group (data not shown).

### 4. What factors influence pretransplant MAIT cell count?

We finally asked if high MAIT cell count is an independent favorable prognostic marker of myeloid aplasia or if a high MAIT cell count identifies patients who would have better prognosis anyway. For example, longer time between the last chemotherapy and ASCT (ref.[17]) and lower age and remission of the disease at the time of transplant[18] are associated with better survival in NHL. Fig. 2 shows that the amount of MAIT cells prior to the ASCT does not correlate with age (Fig. 2A, Spearman's Rho=-0.098, *P*=0.165), sex (Fig. 2B, Student's t-test, *P*=0.486), time from diagnosis to ASCT (Fig. 2C, Spearman's Rho=-0.058, *P*=0.284), time from the last treatment to ASCT (Fig. 2D, Spearman's Rho=0.002, *P*=0.491), number of pretransplant regimens (Fig. 2E, Spearman's Rho=-0.057, *P*=0.288) or clinical outcome pre-Tx – patients in complete or partial remission versus patients in stable or progressive disease (Fig. 2F, Student's t-test, *P*=0.404).

## DISCUSSION

Bacterial infection is the major cause of morbidity and mortality in the early period after hematopoietic stem cell transplantation. The development of the infection is related to two critical factors – duration and depth of neutropenia and disruption of the mucocutaneous barrier, respectively. Both are the direct consequence of conditioning regimens.

Current prophylactic options are restricted to two strategies. These include the use of myeloid growth factors to reduce the depth and duration of neutropenia and the use of prophylactic antibiotics. The use of systemic antibiotic prophylaxis reduces the incidence of febrile episodes, clinically or microbiologically documented infection and bacteriaemia, but has no significant effect on all-cause mortality or infection-related mortality. Moreover, patients with systemic antibiotic prophylaxis have a greater incidence of adverse events[19].

The use of myeloid growth factors after transplant has become a standard of care as they accelerate myeloid recovery and shorten the duration of hospital stay. The growth factors, however, do not have any major impact on clinical variables such as febrile days or septic episodes[20-22].

Given the fact that neither growth factors nor antibiotics ensure safe outcome of myeloid aplasia, it is rational to search for additional factors that could prevent infection and thus reduce morbidity and mortality in this period of ASCT. It seems intuitive to turn the attention to lymphoid lineage given its unique developmental pathway, drug sensitivity, etc. Lee and colleagues, for example, described a correlation between early treatment-related complications and lymphocyte populations of infused autografts or peripheral blood. A lower ratio of infused $CD4^+$ to $CD8^+$ cells was an independent factor for severe mucositis[23] and low proportion of $CD3^+CD4^+CD161^+$ cells in peripheral blood was an independent predictor of mucositis (≥ grade 3), infection before engraftment and CMV activation[24].

Here we showed that a certain anti-infective potential during myeloid aplasia is also provided by MAIT cells. We could only assume that MAIT cells survive the conditioning in the tissues, as any confirmatory invasive procedure is contraindicated due to the deep neutropenia and thrombopenia.

The data suggest that MAIT cells may survive the conditioning as they are resistant to cytotoxic treatment involving anthracyclines[8]. Note that these drugs are usually not part of conditioning regimens prior to the ASCT. On the other hand, MAIT cells exhibit a proapoptotic

propensity suggesting their higher sensitivity and dying upon treatment[25].

The clinical data provide similarly conflicting findings. Not even two observations in autologous transplants provided concordant results. While Abrahamsson and colleagues reported dramatic reduction of MAIT cells lasting at least 2 years after the transplant[26], our study showed relatively early reconstitution of MAIT cells after the ASCT (ref.[12]).

The main difference between Abrahamsson et al. and Novak et al. was the conditioning regimen used. While the immunoablative regimen induced global lymphodepletion lasting 1 year after the transplant[26] myeloablative regimens examined in our study led to only transitory lymphopenia with lymphoid recovery observed as early as twenty days after the transplant.

Similarly heterogenous results are observed in allogenous settings. Bhattacharyya and colleagues[27] reported early increase in MAIT cells as early as day 30 after allo-SCT. In contrast, other investigators reported severe depletion of MAIT cells lasting years after allogenous transplant[28-30].

Another important question is the origin of MAIT cells. They might be either the tissue-resident survivors of cytotoxic treatment or cells re-infused in the graft. The advantage of allogenous settings is that it makes it possible to identify the source of reconstituted MAIT cells by chimerism analysis. Indeed, chimerism studies showed that MAIT cells are nearly exclusively of donor origin[27]. The donor origin of MAIT cells is also suggested in a study Youssef et al.[28].

The graft could be the source of MAIT reconstitution in autologous settings as well. In fact, the three parameters are closely related in autologous settings. Pretransplant peripheral blood MAIT cell count influences both their amounts in the graft and their amount in the blood post transfer[12,27].

One could argue that better clinical course in patients with high amount of MAIT cells might not be the direct effect of MAIT cells. Instead, the MAIT cell count might represent a surrogate marker of general immune competence given by the age, the time from the last cytotoxic therapy to conditioning, the number of pretransplant regimens or the current status of the underlying hematologic malignancy[17,31].

None of these parameters correlated with MAIT cell count. No correlation between age and MAIT cell count reported here seems to contradict our previous study that showed strong correlation between age and MAIT cell count[32]. We hypothesize the MAIT cell count might be influenced by other factors such as interaction with tumor cells, previous cytotoxic treatments and possibly other factors. The interactions among tumor cells, drugs and MAIT cells are currently under investigation in our laboratory.

Various research groups have reported an association between absolute lymphocyte count (either pretransplant in the peripheral blood or as a content of the graft) and long-term prognosis of the underlying malignancy. There is a suggestion that immunocompetent lymphocytes contribute to the surveillance of the malignancy[17,31]. Since MAIT cells are well equipped to control the tumor growth too[33], it would be interesting to research the impact of MAIT cell count on the long-term prognosis and survival. Our study, however, was not designed to follow long-term prognosis, as it included a broad spectrum of diseases with strikingly different biological origins and prognoses and also different conditioning regimens. Nevertheless, this hypothesis is under examination in our laboratory.

Overall, this study work showed that patients with a high amount of MAIT cells pretransplant have a more favorable course of aplasia as measured by peak CRP levels, amount of red blood cell transfusion units and earlier hospital discharge.

## CONCLUSION

The patients with high amount of MAIT cells pretransplant have a more favorable course of aplasia as measured by peak CRP levels, amount of red blood cell transfusion units and earlier hospital discharge.

**Abbreviations:**
ALT, Alanine Aminotransferase; ANC, Absolute Neutrophil Count; ASCT, Autologous Stem Cell Transplantation; AST, Aspartate Aminotransferase; BEAM, BiCNU/Carmustine, etoposide, Ara-C, melphalan; BuMel, Busulphan and melphalan; CR, Complete Remission; CRP, C-reactive Protein; G-CSF, Granulocyte Colony Stimulating Factor; HD-Mel, High-dose melphalan; HL, Hodgkin Lymphoma; ICU, Intensive Care Unit; MAIT, Mucosal Associated Invariant T; MHC, Major Histocompatibility Complex; MR1, MHC-related Molecule 1; NHL, Non-Hodgkin Lymphoma; PD, Progressive Disease; PR, Partial Remission; R/R, Relapsed/refractory; RBC, Red Blood Cell; SD, Stable Disease; TCR, T-cell Receptor.

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**Author contributions:** JN: study conception and design; IKZ, JSB, BB: acquisition of data; IKZ, JSB, BB, TK, JN: analysis and interpretation of data; TK: statistical analysis; JN: drafting of manuscript; All authors read and approved the final manuscript.

**Conflict of interest statement:** None declared.

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