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CORRESPONDENCE

Impact of comorbidities and body mass index on the outcomes of allogeneic hematopoietic cell transplantation in myelofibrosis: A study on behalf of the Chronic Malignancies Working Party of EBMT

To the Editor:

The process of selection of feasibility for transplant in myelofibrosis (MF) is determined by several factors such as age, disease stage, comorbidities, performance status, and donor availability.[1] The Myelofibrosis Transplant Scoring System (MTSS) has emerged as a valuable tool for selecting suitable candidates for transplant in MF. By incorporating patient-, transplant-, and donor-specific variables, the MTSS has proven its effectiveness in stratifying patients at varying risks of non-relapse mortality (NRM) and overall survival (OS). More recently, a CIBMTR/EBMT score has been identified as an effective tool for MF transplant candidates' prognostication. However, it should be noted that the prognostic ability of both scores may be reduced by a lack of information on the presence of comorbidities and body mass index (BMI) prior to the transplant, which was not available in these analyses.[2]

In order to assess the role of comorbidities and BMI in MF patients undergoing transplantation the Chronic Malignancies Working Party (CWMP) of the EBMT performed a retrospective study with the aim to provide more comprehensive and reliable data on the impact of these factors on transplant outcomes and to identify potential areas for improvement in current MF transplantation protocols. The policy of such study is consistent with that previously published.[3] Inclusion and exclusion criteria, definitions, and methodology are available in the supplemental material.

Overall, 4086 patients were included in the final analysis. Patients' characteristics are available in Table S1. Out of 3157 patients with fully reported comorbidity data, 1701 patients (54%) had at least one comorbidity, with pulmonary conditions being the most prevalent (12.7% moderate and 6.8% severe), as documented also in other transplant scenarios.[4] Other comorbidities present in more than 5% of cases were cardiac disorders (8.6%), diabetes (5.7%) and prior-solid tumor (5.4%). An overview of all comorbidities is available in Figure S1.

Concerning the HCT-CI, 1701 (54%) patients had a low (0), 762 (24%) intermediate (1, 2) and 694 (22%) high-risk (≥3) score, respectively. Table S2 reports the clinical characteristics stratified according to different HCT-CI classes. As expected, higher risk class did correlate with increased use of RIC regimens (high risk with 70% vs. 69% and 62% in intermediate, and low risk, respectively), decreased KPS (KPS <80 in 11% vs. 8.1 and 5%). Moreover, the proportion of the splenectomised patients was higher for the high-risk HCT-CI category (14% vs. 9% and 6% in high, intermediate, and low HCT-CI categories, respectively), leading to a lower prevalence of massive splenomegaly (≥15 cm) (17% vs. 22% and 28%). Compared to previous cohorts in which the HCT-CI had been developed and subsequently validated,[5] the prevalence of comorbidities was higher in our study. Overall, these differences underscore a significant shift in the characteristics of the transplant population over time, as transplantation is increasingly considered in older patients with comorbidities.

By univariable analysis, both NRM and OS were statistically associated with HCT-CI risk categories. The 5-year expected NRM was 27% (25%–30%), 33% (29%–36%), and 36% (32%–40%) in low, intermediate, and high-risk HCT-CI groups ($p < .001$), respectively. The 5-year estimated OS was 58% (55%–61%), 52% (47%–56%), and 46% (42%–51%) for the low, intermediate, and high HCT-CI scores, respectively ($p < .001$) (Figure S2). No statistical differences were observed in relapse incidence ($p = .22$), and incidence of grade 2–4 acute GVHD ($p = .056$) or chronic GVHD ($p = .46$) depending on the HCT-CI. Table S3 details the causes of NRM.

After adjusting for other variables well known to be associated with NRM and OS in MF, high-risk HCT-CI was strongly associated with both NRM (HR 1.32, 95% CI 1.12–1.55, $p < .001$) and OS (HR 1.27, 95% CI 1.11–1.46, $p < .001$), relative to patients with a low-risk HCT-CI (score of 0) (Figure S3). Also, splenectomy status did not appear to affect NRM in the context of high HCT-CI class ($p = .95$).

Therefore, the presence of comorbidities continues to play a negative prognostic role on allo-HCT outcomes and should be integrated into the selection process for MF patients undergoing transplantation along with the existing MTSS and CIBMTR/EBMT tools.

A total of 2679 patients had information on BMI at time of transplant: 50 patients were classified as underweight (1.9%), 1318 as normal weight (49.2%), 964 as overweight (36%), and 347 as grade 1 to 3 obese (13%). Median BMI was 24.9 (range, 12.1–46.1). The high prevalence of overweight and obese individuals suggested that patients with robust nutritional reserves were more often considered suitable for transplantation, while cachectic or sarcopenic patients may have had their transplant deferred due to a general tendency among physicians to avoid transplantation in such conditions, generally associated with worse transplant course. As compared to

under-normal weight patients (1368, 51.1%), overweight/obese patients were more frequently males (69% vs. 57%), and had been more frequently exposed to ruxolitinib (40% vs. 34%). Continuous BMI was weakly correlated with all other comorbidities. Aside from a correlation of 0.11 with diabetes, correlations with any other comorbidity did not exceed ±0.07 (Table S4).

Despite differences in comorbidities and patient characteristics between different BMI classes, on univariable analysis, no significant differences were found across the BMI groups in terms of NRM ($p = .5$), OS ($p = .3$), grade II-IV acute GVHD ($p = .73$), or chronic GVHD ($p = .6$). By contrast, a modest difference was found regarding relapse incidence ($p = .031$). Furthermore, within a multivariable model that accounted for other variables known to correlate with NRM and OS in MF, including weight loss before allo-HCT, BMI was determined to have no significant impact on either NRM ($p = .59$) or OS ($p = .41$). Figure 1A,B show the hazard ratio plots of BMI (relative to a reference BMI of 21.75) on OS and NRM respectively, and highlight the very limited impact of BMI on OS and NRM. Likelihood ratio tests also confirm the lack of non-linear effects on both OS ($p = .25$) and NRM ($p = .33$). These findings contrast with the original HCT-CI data, which identified a BMI >35 as a risk factor in both NRM and OS after allo-HCT.[5] In this context, it seems evident that overweight and obese MF patients should not be excluded from a potentially curative life-saving procedure. In MF, overweight or obesity can be associated with milder disease activity, resulting in better nutritional status and suggesting a greater likelihood of improved survival. On the other hand, even patients with lower BMIs can derive benefits from a transplant procedure.

Importantly, evidence of weight loss >10% within 6 months prior to allo-HCT was significantly associated with higher risk of NRM (HR 1.19, 95% CI 1.01–1.39, $p = .042$), and a trend toward shortened OS (HR 1.19, 95% CI 0.96–1.46, $p = 0.108$). Therefore, it seems to be vital to consider transplantation not when the disease is already symptomatic with ongoing weight loss. In this case, the optimization of nutritional status where possible should be considered.

The major strengths of this study rely on the novelty of this information in the largest sample of MF transplant patients, with comprehensive assessment of comorbidities and BMI and significant follow-up. These numbers permit a comprehensive identification of factors associated with allo-HCT outcomes. Nevertheless, it's important to acknowledge some limitations in this study. First, despite adjusting for weight-loss prior to allo-HCT, the conclusions regarding the effect of BMI on mortality were likely also affected by selection effects that could not be modeled. In particular, patients with BMI >35 (i.e., for whom one would expect a clear negative impact on mortality) in this study may have been selected for allo-HCT based on other more favorable disease characteristics or lack of other comorbidities. Second, the study lacks detailed information regarding specific treatments administered for the management of comorbidities and weight loss before transplantation, which could potentially impact allo-HCT results; additionally, the definition of comorbidities lacks an understanding of their functional impact, and there is a current suggestion to include concomitant frailty assessment in cancer patients.[4] Third, the amount of missing data for both main variables and important adjustment factors was substantial. We chose not to exclude patients on the basis of unavailable comorbidity and BMI information (which may have rendered

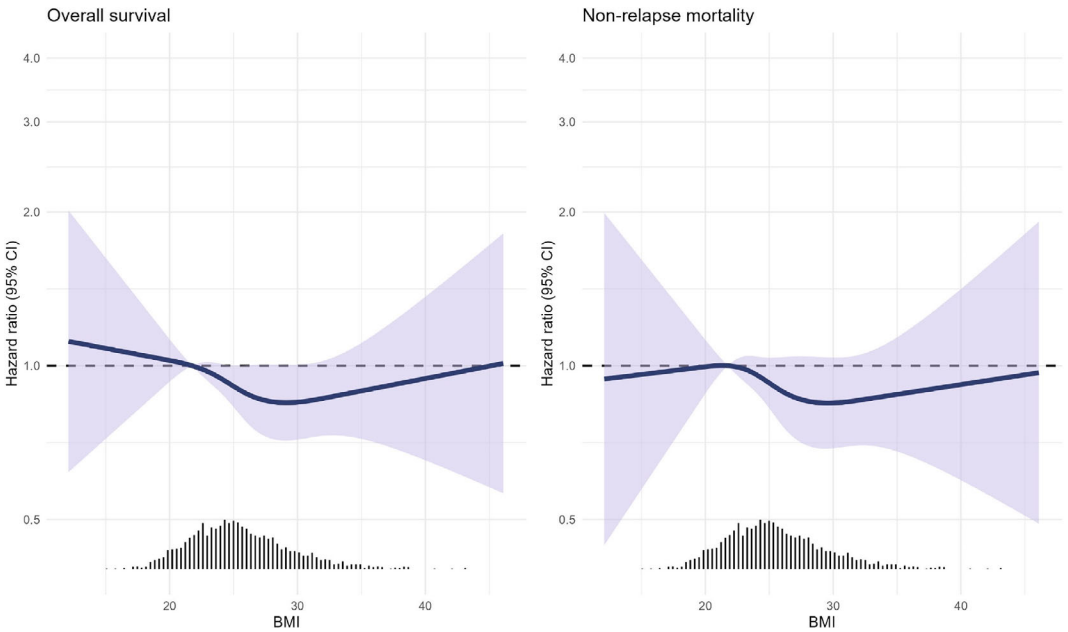

FIGURE 1 Non-linear effect of BMI on overall survival (A) and non-relapse mortality (B) as part of multivariable model adjusting for variables known to be associated with both outcomes in patients with MF. Models are based on $n = 3982$ patients with complete outcome information on OS and NRM, where covariates were multiply imputed using MICE (100 imputed datasets). Displayed are therefore the pooled coefficients. Hazard ratios should be interpreted relative to a reference BMI of 21.75 (mid-point of the "normal" BMI category). The plots also show the (marginal) distribution of observed BMI values.

the cohort less representative), and instead made use of the observed information in the data in order to multiply impute the missing values, thereby potentially enhancing the robustness of the study results. However, the authors believe that despite these limitations, the significance of the topic, which pertains to an ever-growing number of MF patients over the years, outweighs these concerns.

In conclusion, this study, for the first time in a robust fashion, highlights the prognostic significance of HCT-CI in MF patients undergoing allo-HCT. Additionally, it suggests that BMI at the time of transplantation has a limited impact on transplant outcomes in this patient population. These findings enhance our understanding of risk factors and can guide clinical decision-making for MF patients considering allo-HCT. Nevertheless, future research should aim to validate these findings and explore the possibility of integrating comorbidity assessment alongside existing scoring systems and splenomegaly evaluation[3,6] to develop effective tools for selecting MF patients as candidates for transplantation.

AUTHOR CONTRIBUTIONS

NP, DM, JCH, TC, GB conceived and designed the research. NP, EB, LdW, LK, DM, JCH, TC, GB, KR, MR, JD, LA, DR analyzed and interpreted the data. NP and EB wrote the manuscript. NMK, TS, RPL, JP, KS, AB, AC, PD, DB, IYA, SLP, JF, PC, GH, WR, SS enrolled patients in the study and collected data. All authors reviewed the manuscript before submission.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The EBMT only releases de-identified datasets that comply with all relevant global regulations regarding privacy and confidentiality. The data underlying this publication will be made available upon written request to the corresponding author.

PATIENT CONSENT STATEMENT

Each patient provided consent for the collection of data by the EBMT.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.