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Sex-associated differences in outcome of patients with acute myeloid leukemia undergoing allogeneic hematopoietic stem cell transplantation

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TO THE EDITOR:

For many years, females were either underrepresented in clinical studies, or sex was not included as a covariate when reporting outcomes [1]. However, recent research detected sex-associated differences of drug efficacy and toxicity. This was supported by new FDA and NIH policies to ensure the sex-balanced inclusion of patients into clinical trials and to regard sex as a variable in medical research [1, 2]. Sex-chromosomes and hormones contribute to sex-disparities in cancerogenesis as they influence cell metabolism, vulnerability to oxidative stress, and enzymes activity [3]. Additional behavioral differences lead to males being more frequently exposed to cancer risk factors like nicotine and alcohol or weight gain [4]. Subsequently, females in general have lower incidences of malignancies, and lower cancer mortality [5]. However, this also remains true after adjustment for risk behavior and cancerogen exposure [5], suggesting a higher impact of sex as previously assumed. Also, for hematologic neoplasms in general, as well as for acute myeloid leukemia (AML), a lower incidence has been reported for female individuals [6].

In concordance with the generally longer life expectancy in female individuals, most studies in patients undergoing chemotherapy suggested either comparable or longer overall survival (OS) for female AML individuals [7, 8]. However, in these studies, only a minority of AML patients underwent an allogeneic HSCT, limiting our knowledge in this context. The consecutive graft-versus-leukemia (GvL) effect may impact outcomes between sexes differently, as a more pronounced humoral and cellular immunity has been shown in female individuals [9]. Matching this, an association of female sex and longer OS after HSCT has been reported in unselected hematologic neoplasms [10, 11]. Nevertheless, data on sex-disaggregated outcomes in AML patients undergoing HSCT are very scarce, which to evaluate was the main objective of this study.

We analyzed 451 AML patients who underwent allogeneic HSCT after non-myeloablative or reduced intensity conditioning (median age 63, range 22–76 years). Self-reported sex was stratified binarily into female and male, which was congruent with genetic sex in all cases with available cytogenetics ($n = 396$). For patient characteristics see Table 1 and Supplementary Table 1. Details on the applied treatments, and statistical analyses are given in the Supplementary Information. Median follow up after HSCT was 4.2 years.

At AML diagnosis, previous studies already showed distinct characteristics between sexes, especially higher incidences of normal cytogenetics, *NPM1* mutations or *FLT3*-ITD in females, and higher incidences of myelodysplasia-related gene and spliceosome mutations, as in *RUNX1*, *ASXL1*, or *SRSF2*, in male patients [8]. This resulted in female patients more often classified as intermediate, and male patients more often as adverse ELN2022 risk [8]. We also observed an enrichment in male AML patients for spliceosome mutations ($P = 0.02$) and secondary AML ($P = 0.03$)—mostly after myelodysplastic neoplasm—as well as lower blast counts in bone marrow ($P = 0.008$) and blood ($P = 0.004$) at diagnosis [8]. However, the ELN2022 risk stratification did not differ between sexes in our cohort, likely a result of a selection bias for patients undergoing HSCT.

Regarding outcomes after chemotherapy, recent studies suggest a prognostic relevance of patient sex in AML [6, 7]. After HSCT, we observed a shorter time to leukocyte engraftment ($P = 0.03$, Supplementary Fig. S1), similar non-relapse mortality (NRM, $P = 0.96$), but lower CIR ($P = 0.05$) and longer OS ($P = 0.02$, Fig. 1A, B) in female patients as compared to males. In multivariate analyses, female patient sex remained significant for longer OS (Odds Ratio 1.35, $P = 0.03$) after adjustment for conditioning intensity, while CIR was influenced by the ELN2022 genetic risk group and the number of remission at HSCT (Supplementary Tables S2 and S3).

A Korean Study in older individuals (> 60 years) also showed shorter OS due to higher NRM after HSCT for males, but was restricted by a small sample size ($n = 116$) and a combined analysis of MDS and AML patients [12]. Our observed favorable outcomes for females are in accordance with several published studies after chemotherapy, showing longer OS for female AML patients in general [6, 13], as well as in hospitalized individuals [7]. Analyses in pediatric and young adult patients identified the largest outcome differences in favor of the female sex after onset of puberty, which again suggests the importance of sex hormones, while in adults, sex remained a prognostic risk factor irrespective of older age (and subsequent menopause) [13, 14]. In contrast, few other studies failed to show OS differences after chemotherapy for reasons not fully understood [8]. Finding a distinct prognostic relevance of sex in two large patient sets treated in the USA (similar outcomes) and Germany (longer OS in female patients) Ozga et al. speculated that the choice of HSCT as consolidation may modulate outcome differences in favor of the female sex [8].

On the other hand, the observed distinct outcomes in our study might be influenced by additional HSCT-related factors differentially present in female vs male patients. Following the EBMT recommendation, male patients in our cohort were less often transplanted from a female donor ($P = 0.004$). However, recent studies suggested that OS-differences after HSCT were driven by

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Table 1. Patients' characteristics.

	all patients *n* = 451	**female patients *n* = 216 (48%)**	**male patients n = 235 (52%)**	***P***
Age at HSCT, years				0.13
median (range)	63.14 (27.22–76.78)	62.6 (27.22–76.78)	63.95 (31.3–76.4)	
Disease origin, *n* (%)				
secondary	136 (30)	48 (22)	88 (37)	<0.001
therapy-related	42 (9)	26 (12)	16 (7)	0.07
de novo	273 (61)	142 (66)	131 (56)	0.03
Hemoglobin, g/dL				
median (range)	8.7 (3.2–15.68)	8.5 (4.5–15.68)	8.9 (3.2–15.3)	0.06
Platelet count, x 10^9/L				
median (range)	65 (1–950)	64 (9–950)	65 (1–501)	0.71
WBC, x 10^9/L				
median (range)	4.4 (0.1–385)	5.3 (0.1–366)	3.7 (0.6–385)	0.72
Blood blasts, %				
median (range)	16.5 (0–97)	22 (0–96)	11 (0–97)	0.004
Bone marrow blasts, %				
median (range)	50 (3–95)	56.5 (3–95)	42 (4.6–95)	0.008
CD34 + /CD38- cell burden				
median (range)	0.7 (0–89)	0.6 (0–63)	0.7 (0–89)	0.36
LDH, ukat/l				
median (range)	5.37 (1.4–49.7)	5.4 (1.4–33.64)	5.37 (2.52–49.7)	0.72
Normal karyotype, *n* (%)				
absent	205 (49)	91 (46)	114 (52)	0.20
present	211 (51)	107 (54)	104 (48)	
Complex karyotype, *n* (%)				
absent	349 (87)	164 (87)	185 (88)	0.84
present	51 (13)	25 (13)	26 (12)	
ELN2022 risk, *n* (%)				0.35
favorable	64 (22)	38 (26)	26 (19)	
intermediate	75 (26)	39 (26)	36 (26)	
adverse	148 (52)	72 (48)	76 (55)	
ASXL1 mutation, *n* (%)				0.61
wild type	124 (88)	63 (90)	61 (86)	
mutated	17 (12)	7 (10)	10 (14)	
CEBPA mutation, *n* (%)				0.49
wild type	267(88)	135 (89)	132 (86)	
mutated	39 (13)	17 (11)	22 (14)	
FLT3-ITD mutation, *n* (%)				0.26
wild type	277 (82)	134 (79)	143 (85)	
mutated	61 (18)	35 (21)	26 (15)	
FLT3-TKD mutation, *n* (%)				0.29
wild type	291 (93)	143 (91)	149 (94)	
mutated	23 (7)	14 (9)	9 (6)	
IDH1 mutation, *n* (%)				0.07
wild type	239 (90)	118 (88)	121 (91)	
mutated	28 (9)	16 (12)	12 (9)	
IDH2 mutation, *n* (%)				0.35
wild type	229 (85)	115 (85)	114 (86)	
mutated	39 (15)	20 (15)	19 (14)	
NPM1 mutation, *n* (%)				0.67
wild type	155 (65)	122 (72)	133 (79)	
mutated	82 (35)	47 (28)	35 (21)	
RUNX1 mutation, *n* (%)				>0.99
wild type	115 (82)	57 (83)	58 (82)	
mutated	25 (18)	12 (17)	13 (18)	
SRSF2 mutation, *n* (%)				0.04
wild type	107 (82)	55 (90)	52 (75)	

Table 1. continued

	all patients $n = 451$	female patients $n = 216$ (48%)	male patients n = 235 (52%)	*P*
mutated	23 (18)	6 (10)	17 (25)	
Spliceosome mutation*, *n* (%)				0.02
wild type	98 (67)	51 (77)	47 (59)	
mutated	48 (33)	15 (23)	33 (41)	
TP53 mutation, *n* (%)				0.61
wild type	123 (89)	60 (87)	63 (90)	
mutated	16 (11)	9 (13)	7 (10)	
Remission status at HSCT, *n* (%)				0.49
CR/CRi 1	352 (79)	171 (80)	181 (78)	
CR/CRi 2	95 (21)	42 (20)	53 (23)	
MRD status at HSCT, *n* (%)				0.39
negative	53 (60)	31 (65)	22 (54)	
positive	36 (40)	17 (35)	19 (46)	
Conditioning regimen, *n* (%)				0.58
nma	389 (86)	184 (85)	205 (87)	
ric	62 (14)	32 (15)	30 (13)	
In vivo T cell depletion, *n* (%)				0.48
no	394 (87)	186 (86)	208 (89)	
yes	57 (13)	30 (14)	27 (11)	
HCT-CI Score, *n* (%)				0.004
0	176 (40)	98 (47)	78 (34)	
1/2	126 (29)	46 (22)	80 (36)	
≥ 3	133 (31)	67 (32)	66 (29)	
Donor type, *n* (%)				0.41
matched related	68 (15)	32 (15)	36 (15)	
unrelated, HLA matched	272 (60)	135 (63)	137 (58)	
HLA mismatched	102 (23)	43 (20)	59 (25)	
haploidentical	9 (2)	6 (3)	3 (1)	
Donor sex, *n* (%)				0.004
female	146 (33)	84 (39)	62 (26)	
male	300 (67)	129 (61)	171 (73)	
CMV status, *n* (%)				0.14
recipient + / donor –	166 (37)	72 (33)	94 (40)	
all others	282 (63)	143 (67)	139 (60)	
Acute GvHD ≥ grade 2, *n* (%)				0.86
absent	216 (55)	108 (57)	108 (52)	
°I	72 (18)	34 (18)	38 (18)	
°II	37 (9)	18 (9)	19 (9)	
°III	48 (12)	20 (11)	28 (14)	
°IV	23 (6)	10 (5)	13 (6)	
Chronic GvHD, *n* (%)				0.003
absent	114 (36)	46 (30)	68 (43)	
limited	49 (16)	34 (22)	15 (9)	
extended	152 (48)	75 (48)	77 (48)	

*Spliceosome mutation, comprising mutations in SRSF2, SF3B1, U2AF1 and ZRSR2.
ASXL1 Additional Sex Combs-Like gene1, *CEPBA*, *CCAAT* enhancer-binding protein alpha gene, *CMV* cytomegalovirus, *CR* complete remission, *CRi* complete remission with incomplete peripheral recovery, *ELN* European Leukemia Net, *FLT3* fms-like tyrosine kinase, *FLT3-ITD* internal tandem duplication of the FLT3 gene, *FLT3-TKD* tyrosine kinase mutations in the FLT3 gene, *GvHD* graft-versus-host disease, *Hb* hemoglobin, *HCT-CI* hematopoietic cell transplantation comorbidity index, *HLA* human leukocyte antigen, *HSCT* hematopoietic stem cell transplantation, *IDH* isocitrate dehydrogenase gene, *LDH* lactatedehydrogenase, *MRD* measurable residual disease, *nma* non-myeloablative, *NPM1* Nucleophosmin 1 gene, *PB* peripheral blood, *ric* reduced intensity conditioning, RUNX1, RUNX family transcription factor 1 gene, *SRSF2* serine and arginine rich splicing factor 2 gene, *WBC* white blood cell count.

recipient sex, rather than a certain recipient-donor sex constellation [10, 11]. This was also the case in our study, as we did not observe adverse outcomes in male patients receiving stem cells from a female *vs* a male donor (CIR $P = 0.61$, NRM $P = 0.24$, and OS $P = 0.90$, Supplementary Fig. S2).

In our cohort, female patients more frequently developed a chronic Graft-versus-Host-Disease (GvHD, $P = 0.003$). This somewhat matches the higher incidence of autoimmune diseases in female individuals, especially connective tissue diseases, which is also a frequent manifestation of chronic GvHD. Despite the higher

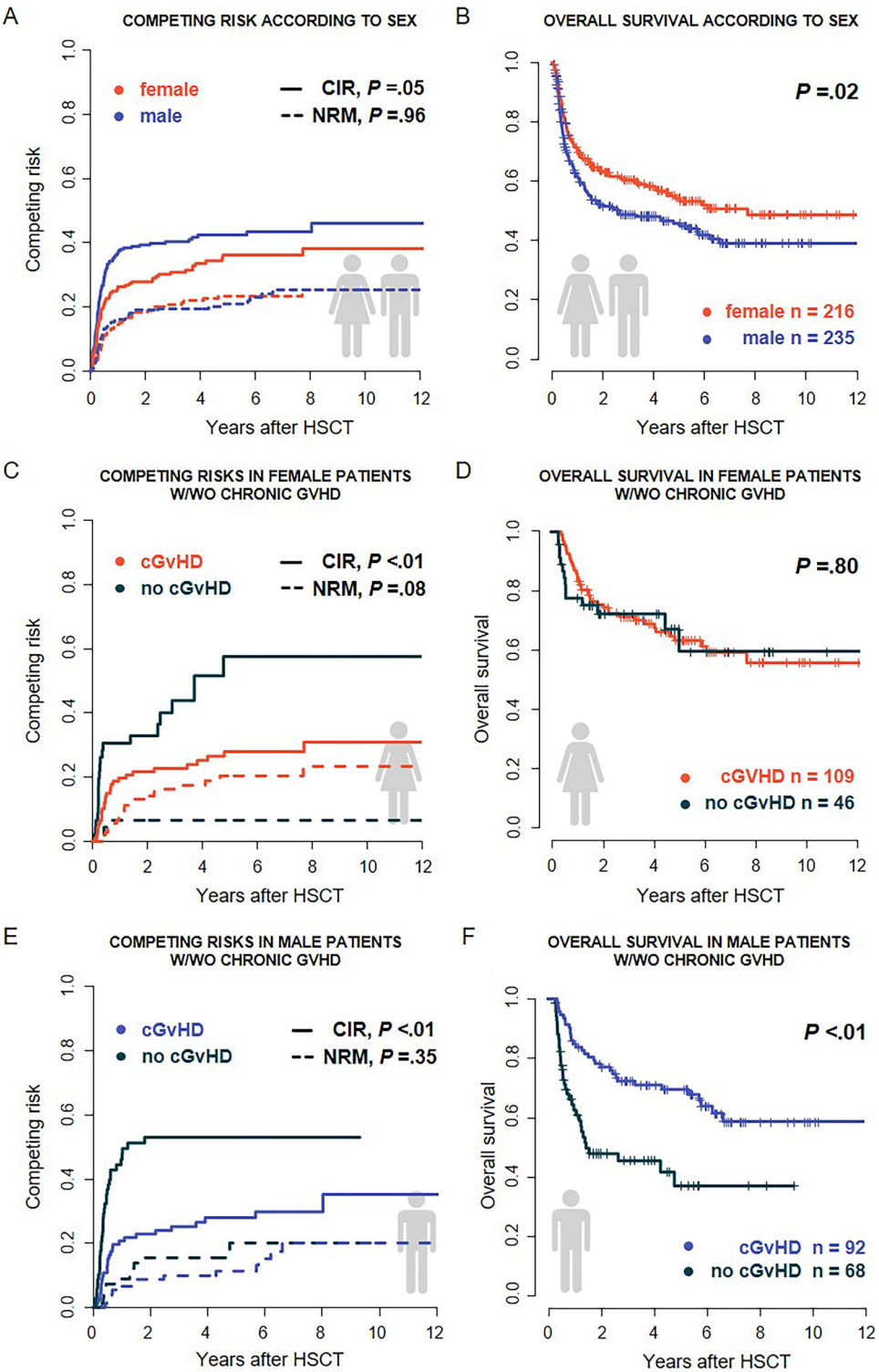

Fig. 1 Outcomes after HSCT according to patient sex (A,B) as well as according to the development of a chronic GvHD (day 100 landmark, C-F). A Competing risk analysis for non-relapse mortality (NRM) and cumulative incidence of relapse (CIR) and **B** Overall survival (OS) according to patient sex for the whole patient cohort. **C** NRM and CIR and **D** OS according to the development of a chronic GvHD in female patients. **E** NRM and CIR and **F** OS according to the development of a chronic GvHD in male patients.

incidence of chronic GvHD in women, outcomes of male patients seemed to depend more on the GvL effect after HSCT, as only male patients developing chronic GvHD had favorable outcomes comparable to those of female patients (Fig. 1C–F).

In patients alive longer than 5 years after HSCT, Islam et al. observed a slightly higher incidence of chronic GvHD in males (55 *vs* 49%) [10], which might further underline the higher need for a chronic GvHD in male compared to female patients to reach long-term OS after HSCT. In our study, the development of an acute GvHD was associated with a higher NRM and subsequently shorter OS in both, female and male patients (Supplementary Fig. S3). However, while the frequency and severity of acute GvHD was

similar between sexes ($P = 0.86$, Table 1), male patients developing an acute GvHD had a shorter OS than female patients developing an acute GvHD, potentially indicating a higher vulnerability from alloimmune reactions in males. In line with these results, in male, but not in female patients, the use of a matched sibling donor (MSD)—known to result in the lowest risk of a chronic GvHD—was associated with a significantly higher CIR, while the use of a mismatched unrelated donor (MMUD)—known to result in the highest risk of acute GvHD – was associated with a significantly higher NRM (Supplementary Fig. S4). Subsequently, the use of a matched unrelated donor (MUD) was of high clinical relevance in male patients, as it resulted in a trend toward longer OS compared to MSD or MMUD ($P = 0.06$, Supplementary Fig. 4SF).

The measurable residual disease (MRD) status prior to HSCT has been identified as an important prognostic factor [15], but so far, there is no data available that evaluates MRD with respect to patient sex. In a sizeable subset of patients, we were able to evaluate molecular MRD based on the long-established marker *NPM1* [15] or *RUNX1*, which also functions as a reliable MRD marker as we recently showed (EHA 2022). Here, the MRD status in remission prior to HSCT was predictive for CIR and OS (Supplementary Fig. S5), irrespective of patient sex.

Overall, available data analyzing the efficacy of treatment modalities with patient sex as a relevant cofactor falls short behind what should be expected in modern and evidence-based medicine. We believe that it is of utmost importance to work towards more sex-sensitive approaches in research, and incorporate the results in our medical practice to allow for individualized health care. Some studies testing new drugs are already beginning to show subgroup analyses of drug efficacy according to sex, for which trials testing FLT3 inhibitors in AML are recent examples.

Our retrospective single-center study has clear limitations, including the restriction to patients receiving non-myeloablative or reduced intensity conditioning, the molecular and MRD data being available only in a subset of the cohort, and small patient numbers in subgroup analyses. Our results point to a distinct relevance of immunologic effects after HSCT between female and male AML patients. When confirmed as part of prospective trials or larger databank-based cohorts our results may influence the donor choice, as prefering an MUD over MRD in male patients. In addition, future studies should focus on ways to adjust immunosuppression, as in vivo T cell depletion may have distinct clinical impact in male or female patients. While conclusive explanations for the observed distinct efficacy of chemotherapy, targeted treatments and immunologic effects—as those after HSCT—observed by us and others are lacking, these data represent an important first step to better understand sex-associated outcome differences in AML.

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DATA AVAILABILITY

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

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AUTHOR CONTRIBUTIONS

J.U. and M.J. contributed to the design and analysis of this study and the writing of the manuscript, and all authors agreed on the final version. M.J., L.B., J.J., J.U., D.Br., D.b.a., J.J. and S.S. carried out the laboratory-based research; M.J. and J.U performed statistical analyses; and M.M., G.N.F., V.V., K.H.M., M.H., U.P. and S.S. provided structural support.

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COMPETING INTERESTS
The authors declare no competing interests.

ETHICS APPROVAL
Data analyses were approved by the Institutional Review Board of the University Hospital Leipzig (305/23-ek).

PATIENT CONSENT
Written informed consent was obtained in accordance with the Declaration of Helsinki.

ADDITIONAL INFORMATION
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