

# A multicenter comparative acute myeloid leukemia study: can we explain the differences in the outcomes in resource-constrained settings?

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## Introduction

Acute myeloid leukemia (AML) are heterogeneous aggressive ARTICLE HISTORY Received 26 July 2020 Revised 5 September 2020 Accepted 18 September 2020 KEYWORDS Acute myeloid leukemia; survival; early mortality; infection; stem-cell transplant [5,6], there is a paucity of published data on AML outcomes in such healthcare settings. leukemias with poor prognosis. Determinants of poorer outcomes include increased age, poor performance status, high white blood cell (WBC) counts at presentation, adverse cytogenetic cmolecular risk, and secondary AML (i.e. antecedent myeloid malignancy) [1]. Socioeconomic factors may also impact on AML cure rates as even in economically developed nations; there are significant disparities [2,3]. Eighty-five percent of the world's population live in low- and middle-income countries (LMIC) [4]. Despite previous reports that poor resources limit accurate diagnosis and effective treatment of AML Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option for patients with higher risk AML. It is indicated as consolidation in first complete response (CR1) for patients with intermediate and adverse genetic risk [7]. However, HSCT is costly: it increases inpatient stays and doubles treatment costs [8]. In a Brazilian study [9], only 5% of patients in a multicenter cohort underwent HSCT in CR1, compared to 50% in a university hospital in France [10]. Supportive care is crucial for patients undergoing intensive chemotherapy (ICT) and HSCT. Infection is a major cause of death in AML patients [11]. There has been improvement in prophylaxis and prompt management of these events in high-income countries [12], but this remains a major challenge in resource imited settings [13,14]. To our knowledge, no published study has directly compared AML outcomes between centers from economically developed countries and those with emerging economies. To better understand biological and clinical drivers of outcomes, we performed a retrospective analysis comparing patient demographics, disease-risk classifiers, treatment and survival of adult AML patients in Brazil and in the UK.

## Methods

Patients and treatment Three cohorts were composed of 167, 145, and 157 consecutive adults (range: 16–65 years old) diagnosed with AML, eligible to intensive CT, between October 2001 and February 2018 at University of Sao Paulo (USP) medical school hospitals: Faculdade de Medicina da Universidade de S~ao Paulo (FMUSP) and Faculdade de Medicina de Ribeir~ao Preto (FMRP), and at Oxford University Hospitals (OUH), respectively (Supplementary Methods Figure 1). Cohorts are referred to by their hospital acronyms. AML was defined using World Health Organization criteria [15]. This study was approved by institutional review board for Brazilian cohorts (CAAE: 80673316.3.0000.0068 and 33923820.2.0000.5440). Anonymized clinical data collection for the UK cohort has been carried out according to local guidelines and did not require ethical board review. All patients received intensive induction regimens, typically Daunorubicin (60 or 90mg/m2 for

three days), and Cytarabine (100 or 200mg/m<sup>2</sup> for 7 or 10 days) following local institutional protocols. Most OUH patients received two courses of Daunorubicin plus Cytarabine induction. Consolidation therapy consisted of ICT with Cytarabine (1.5g/m<sup>2</sup> or 3g/m<sup>2</sup> for three days (HiDAC)) and/or allogeneic HSCT performed according to clinical judgment, donor availability, and bed capacity. Patients in FMUSP and FMRP were not prescribed antibacterial or antifungal prophylaxis routinely prior to 2016. After that, in FMUSP prophylactic ciprofloxacin and anidulafungin were used in neutropenic patients, and in FMRP, fluconazole was given for the same indication. Anidulafungin has in vitro activity against aspergillus with unproven clinical efficacy and is inactive against fusarium or mucormycosis [16]. In OUH, fluconazole prophylaxis was used routinely, with anti-aspergillus agents (voriconazole or posaconazole) reserved for secondary prophylaxis until 2013, after which these agents were used for primary prophylaxis. Acyclovir prophylaxis was routinely used in all centers. Infection endpoints were collected from medical records, and infection events and organ definitions according to the treating physician annotations, laboratory, radiological and culture records. Multidrug resistant (MDR) was defined as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories [17]. Febrile neutropenia and other complications were managed according to hospital guidelines, and the practice of the attending hematologist. HSCT, but not induction therapy, was routinely performed in hepa-filtered rooms in all three centers. A key difference between practice in Brazil and in Oxford during the period covered by this study is that empirical anti-aspergillus therapy is commenced in cases of persistent fever despite antibiotics within 3–5 of presentation, whereas radiological evidence of aspergillus is routinely sought prior to systemic antifungal therapy in Brazil. Clinico-pathological data, cytogenetics and molecular classification, response and outcome definitions Clinical and laboratory data were collected by review of electronic medical records and computer databases. Samples for genetic analyses were obtained at diagnosis and processed in reference laboratories of each participating center. Cytogenetic analyses were performed on bone marrow aspirates according to standard techniques for chromosomal banding. Bone marrow (preferentially) or peripheral blood were used for molecular analyses. Polymerase chain reaction (PCR) techniques followed by standard electrophoresis and fragment analysis methods were performed for the detection of FLT3-ITD, NPM1, and CEBPA mutations [18–20]. Where there was sufficient data, patients were assessed using the cytogenetic-molecular adapted genetic risk (AGR) for all three cohorts (Supplementary Methods Figure 2)[21]. Patients were stratified as favorable-risk (FR), intermediate-risk (IR) or adverserisk (AR). Response criteria followed ELN2017 recommendations [22]. Early mortality (EM) was defined as death within the first 60-days of treatment without reaching CR1 [23], and non-relapse mortality (NRM) when a patient died after achieving CR1 without documented relapse during the study follow-up (FUP) time. EM was annotated with a cause based on clinical documentation of infection, grade 5 toxicities (e.g. hepatotoxicity, heart failure), and bleeding. A patient was refractory if a complete response (CR) was not achieved after two courses of ICT. Statistical analysis and modeling Continuous variables were described as median and interquartile range (IQR) and differences between cohorts were assessed using the Wilcoxon rank-sum test. Differences in categorical variables between cohorts for both were assessed either using chisquared or Fischer's tests when appropriate. Cutoffs for continuous variables were modeled as previously described [21]. Overall survival (OS) was calculated as the difference in months between diagnosis and last FUP date, and disease-free survival (DFS) between CR date and either relapse or last FUP

date (whichever occurred first). Survival measures and curves were estimated using the Kaplan–Meier (KM) and group comparisons with a log-rank test. We also performed a cumulative incidence estimation for HSCT, with death as the competitive event and using three endpoints: ‘all HSCT’ (time from diagnosis until HSCT or last FUP); HSCT in CR1 (only for patients with AGR IR or AR AML, with time from CR/CRi until HSCT or last FUP); and HSCT in second complete remission (CR2) (patients who relapsed and achieved CR2, with time from relapse date to HSCT or last FUP). A cumulative incidence of relapse (CIR) was estimated as the occurrence of relapse from the CR/CRi date until relapse date or last FUP, again, having death as a competitor event (i.e. cumulative incidence of NRM as competitor). The group comparison for the cumulative incidence functions was computed using Gray’s test. Another survival analysis was performed for patients who relapsed taking the relapse date until last FUP. Multivariate Cox proportional-hazard model (CPHM) was performed for OS and DFS as outcomes on two occasions. First, after comparing both USP (FMUSP and FMRP) cohorts variables to adjust them to any heterogeneous predictor ( $p < .05$ ) in order to assess whether it would be feasible to merge them into a single cohort. Second, in the final model where we compared the two Brazilian cohorts with OUH adjusting the treatment center to again all differences in patients’ variables. To decide which of those variables to include in the model, we performed a stepwise selection in all variables assessed as heterogeneous in the group comparisons per cohort ( $p < .05$ ), yet measuring the fitness and getting the best model as Akaike information criteria (AIC) [24]. The induction schema was not included in any of those analyses due to its biased retrospective nature. Statistical significance was set as  $p$  value  $< .05$ . All statistical analysis and modeling were performed in R version 3.6.1 (The CRAN project, [www.r-project.org](http://www.r-project.org)).

## Results

Characteristics and clinical outcome of two Brazilian AML cohorts At baseline, patients from FMUSP and FMRP differed in age ( $p = .01$ ), WBC counts ( $p = .049$ ), and AML origin (de novo vs. secondary) ( $p = .01$ ) (Supplementary Results Table 1). After adjusting for these variables, there was no statistical difference in OS (5 years: 29.6% vs. 28%,  $p = .6$ ; HR  $\approx 1.1$  (0.84–1.5),  $p = .48$ ) and DFS (5 years: 32.3% vs. 28.5%,  $p = .78$ ; HR  $\approx 0.99$  (0.7–1.4),  $p = .96$ ) (Supplementary Results Figure 1A–D). For clarity of comparison with the UK OUH cohort, we merged FMUSP and FMRP cohorts ( $N = 312$ , referred to as ‘USP’). Clinical characteristics of AML patients in USP and OUH cohorts Baseline characteristics of USP and OUH cohorts are heterogeneous and summarized in Table 1. Compared with OUH, USP patients were younger (median 45 vs. 51.4 years,  $p < .001$ ) and had lower albumin levels (median 3.6 vs. 4.1 g/dL,  $p < .001$ ). Although WBC counts ( $p = .14$ ) were similar in both cohorts, hemoglobin and platelets were higher in OUH ( $p < .001$ ). Patients’ cytogenetic-molecular risk was assessed using the novel AGR [21]. AGR is a genetic risk assessment that enables accurate prediction despite some missing diagnostic data. We were able to classify 305/ 312 patients in USP and 139/158 in OUH (Table 1). There was a non-statistically significant trend for lower genetic risk in USP where (29.5% FR vs. 20.5% in OUH,  $p = .08$ ) and fewer secondary cases in USP (5% vs. 12% in OUH,  $p = .002$ ). Post-remission therapy and stem-cell donor were significantly different between cohorts (Table 1), in particular, USP performed threefold fewer allogeneic HSCT than OUH ( $p < .001$ ). Unadjusted overall and disease-free survival for AML Median FUP times were 59.4 and 72.2 months for USP and OUH, respectively. Patients from USP had shorter OS (median of 12.3 vs. 51.6 months in OUH,  $p < .001$ ). Five-year OS was 29% (USP) vs. 48.5% (OUH) ( $p < .001$ , Figure 1(A)). USP also had decreased median

DFS (10.3 vs. 21.2 months), and 5-year DFS (30.7% vs. 35%,  $p = .01$ , Figure 1(B)). Difference in unadjusted DFS is less than OS as DFS removes the effect of EM by only considering patients who attained CR. Adjusting for factors affecting overall and disease-free survival To adjust just for confounding factors between cohorts, we performed a CPHM for OS and DFS, including HSCT as a time-dependent variable and the AGR assessment [21]. For OS, the following factors were considered: HSCT (as a time-dependent variable), older age ( $>45$ -years) (HR 1.36, 95% CI: 1.05–1.75;  $p = .018$ ), very low or high WBC (high-risk:  $<1.5$  or  $>30.0 \times 10^3/\text{mm}^3$ ) (HR 1.63, 95% CI: 1.28–2.09;  $p < .001$ ), and AGR IR (HR 1.58, 95% CI: 1.14–2.18;  $p = .006$ ) or AR (HR 2.72, 95% CI: 1.95–3.96;  $p < .001$ ) (Figure 2(A)). However, higher albumin at diagnosis ( $>3.8 \text{ g/dL}$ ) (HR 0.37, 95% CI: 0.28–0.5;  $p < .001$ ), HSCT (HR 0.58, 95% CI: 0.43–0.79;  $p < .001$ ), and having OUH as treatment center (HR 0.69, 95% CI: 0.51–0.95;  $p = .027$ ) were associated with increased OS (Figure 2(A)).

A multivariate model for DFS showed that secondary AML (HR 2.01, 95% CI: 1.14–3.55;  $p = .016$ ), and AGR IR (HR 1.51, 95% CI: 1.05–2.18;  $p = .024$ ) or AR (HR 2.74, 95% CI: 1.78–4.23;  $p < .001$ ) were associated with inferior outcome, whereas higher albumin ( $>3.8 \text{ g/dL}$ ) (HR 0.56, 95% CI: 0.41–0.76;  $p < .001$ ) and HSCT (HR 0.24, 95% CI: 0.16–0.36;  $p < .001$ ) were protective. Interestingly, after adjustment for confounders, including the effect of a higher proportion of HSCT in CR1 in OUH, the treatment center per se did not have a significant impact on DFS (HR 1.39, 95% CI: 0.93–2.12,  $p = .102$ , Figure 2(B)).

Cumulative incidence of hematopoietic stem cell transplantation. Since HSCT appears to be predictive for survival, we assessed the time taken for treatment centers to perform HSCT. Assuming HSCT would be recommended based on disease risk criteria in 60–70% of AML patients, we performed a cumulative incidence analysis with HSCT as the event and any cause of death as competitors. For all HSCT (encompassing HSCT in 1st and 2nd CR), USP patients proceeded to HSCT significantly later (median: 23.8 (95% CI: 17.5 not reached (NR)) vs. 7.2 months from diagnosis for OUH (95% CI: 6.5–9.1)). Moreover, while USP patients had a 2-year cumulative incidence of HSCT (CI-HSCT) of 51% (95% CI: 42–59%), OUH took 10 months to perform HSCT in 63% of patients and had a 2-year CI-HSCT of 80% (95% CI: 72–86%,  $p < .001$ , Figure 3(A)). When considering HSCT in CR1 for patients with intermediate- or adverse-risk AML, USP centers did not achieve median cumulative incidence, whereas OUH reached the median at 6.9 months after CR1 (95% CI: 6.2–8.2). By 12 months USP had performed HSCT in 23% (95% CI: 15–31%) of IR or AR-AML CR1 patients, while OUH in 70% (95% CI: 59–79%,  $p < .001$ , Figure 3(B)). In contrast, in relapsed and CR2 (2nd CR) patients, median CI-HSCT was 7.9 (95% CI: 5.0–14.4) and 4.4 months (95% CI: 3.4–5.8) for USP and OUH, respectively. At 12 months, USP and OUH had transplanted 69% (95% CI: 43–83%) and 94% (95% CI: 66–99%) of patients, respectively ( $p = .005$ , Figure 3(C)). Finally, subgroup analysis showed that among CR1 matched-related donor (MRD) HSCT patients there was no significant difference in OS between USP (median: NR, 95% CI 34.7 months–NR; 5 years 74%, 95% CI 61–90%) and OUH (median: NR, 95% CI NR; 5 years 54%, 95% CI 38–74%) ( $p = .16$ , Figure 3(D)).

Response rates, cumulative incidence, and survival after relapse Despite similar induction therapy and more FR patients, USP had a 17% lower CR/CRi rate compared with OUH ( $p < .001$ ), but a sixfold higher rate of induction death and similar rates of refractory disease (Table 2). In addition, USP presented a higher CIR with a median and 5-year for USP and OUH patients of 15.7 months/60% and 54.6 months/50%, respectively ( $p = .0022$ , Figure 4(A)). However and interestingly, when comparing patients who performed the same modality of post-remission therapy (ICT or MRD HSCT), there was neither difference in CIR between USP and OUH patients who underwent ICT in CR1 with a median and 5-years CIR of 10.3 months/70%

and 12.9 months/84% for USP and OUH, respectively ( $p=0.55$ , Supplementary Results Figure 2A); nor after HSCT in CR1 where the median was not reached for any cohort and 5-years CIR were 26% and 27% for USP and OUH, respectively ( $p=0.68$ , Supplementary Results Figure 2B). Outcome for patients after relapse was particularly poor in USP. Compared with OUH, median survival was 2.7 vs. 11.7 months, and 3-year survival was 10% vs. 39% ( $p<0.001$ , Figure 4(B)). In USP, out of 108 relapsed patients, 92 (85%) were considered for salvage therapy, from which 44 (47.8%) achieved a CR2, 24 (26%) died without having their bone marrow evaluated, and 24 (26%) were refractory. From those 44 CR2 patients, 34 (77%) were submitted to HSCT, but they were in a slow timing when compared with OUH ( $p=0.005$ , Figure 3(C)). Early mortality and non-relapse mortality Early mortality was fourfold higher for USP patients (23%) compared with OUH (6%,  $p<0.001$ ). However, this was due to induction death (19% USP vs. 3% OUH) rather than primary refractory disease (4% USP vs. 3% OUH) (Table 2). Whereas infection was the main cause (77% of USP EM cases, mainly Gram-negative bacteria (GNB) and invasive fungi), disease refractoriness accounted for 44% of EM in OUH ( $p=0.003$ ) (Table 2). MDR species were cultured in 22 (78.5%) cases of USP patients with GNB infection. Nineteen (86.4%) were isolated in blood (*Klebsiella pneumoniae* 8 (43%); *Pseudomonas aeruginosa* 7 (37%); *E. coli* 2 (10%); *Serratia marcescens* 1 (5%); *Acinetobacter baumannii* 1 (5%)), and 3 (13.6%) in tracheal aspirate (all *Acinetobacter baumannii*). Of the 12 USP patients with fungal infection, three species were commonly detected: (i) *Aspergillus* (50% one case of disseminated aspergillosis in blood culture, and five cases of pulmonary aspergillosis confirmed radiologically and with positive galactomannan tests, with further isolation of *aspergillus* in bronchoalveolar lavage culture or biopsy in 3/5 cases); (ii) *Candida* (33% all four cases isolated in blood culture), and (iii) *Fusarium* (17% 2 cases, isolated in blood culture) (Table 2). In contrast, our cumulative incidence of NRM found no difference between the treating centers where the median CI of NRM was not reached and the 5-years were 24% and 29% for USP and OUH, respectively ( $p=0.84$ , Supplementary Results Figure 3A). Nonetheless, patients in USP were more likely to die after achieving CR/CRi than patients from OUH (Supplementary Results Figure 3B).

**Discussion** We found a substantial difference in survival rates between two cohorts of intensively treated AML patients from two countries with contrasting health economies. Although baseline characteristics in USP patients (age, genetic risk profile, fewer secondary AML) would predict better outcomes, USP patients had worse OS. There is no difference in rate of refractory disease following ICT between the centers. After adjusting OS for patient and disease confounders, and rates of allo-HSCT, OUH still has a 31% hazard-ratio reduction, suggesting that other factors were important in influencing patient outcomes. Rates of CR/CRi in USP patients were lower despite similar therapy as OUH patients, mainly because more patients died during induction (19% vs. 3%). Most induction deaths at USP were due to multi resistant Gram-negative and fungal infection. Although we did not specifically address this in our study, it may be that problems accessing urgent medical attention and higher rates of co-morbidity may contribute to this excess mortality [3,5]. Excess mortality due to infection is potentially preventable by improved patient education, access to high-quality emergency healthcare and prompt administration of antibiotics with activity against causative organisms [13]. Antibacterial prophylaxis has been recommended for neutropenic patients to reduce risk of sepsis, yet evidence regarding efficacy has been mixed. In the UK, fluoroquinolones are recommended based on meta analysis [25]; however, implementation is variable across centers. There are concerns about *Clostridium difficile* and driving antibiotic resistance. Gut colonization by multi-resistant GNB reduces survival in leukemia

and HSCT patients[26], and we suspect that since most of the identified organisms were enterobacteria, the gut is the likely source of the majority of MDRGNB sepsis in our patients. Use of appropriate antibiotics with reference to and local resistance profiles and appropriate access to isolation nursing, high dependency, and intensive care support would also be helpful [27]. Antifungal prophylaxis for both candidemia and aspergillosis was not standard practice in Brazilian centers during the study period. Although established in literature [28], primary prophylaxis against aspergillosis remains suboptimal in Brazil. Also, anti-candida prophylaxis was only adopted from 2016 in our Brazilian centers. A prospective multicenter survey in Brazil found a high cumulative incidence of invasive fungal disease among AML and HSCT patients [29], which reinforces the urgent need to implement better fungal prophylaxis. CIR was higher in USP. After adjustment for confounders, the treatment center per se did not impact DFS, suggesting that HSCT factors rather than disease biology was negatively impacting USP outcomes. Effectiveness of post-remission consolidation itself was not a factor since patients undergoing the same consolidative treatment had similar CIR and similar overall NRM mortality in both cohorts. Allogeneic HSCT is the only curative option for many AML patients [7], and the effectiveness of MRD HSCT delivered in CR1 is similar in OUH and USP. However, our analysis strongly suggests that low HSCT rates and long wait times affect survival of AML patients in USP. We found that USP centers transplanted fewer patients than OUH (28% vs. 75%). Furthermore, the time to transplant was prolonged and failed to reach the predicted optimum number of cases. Compared with OUH, USP is more likely to transplant patients in CR2 even when HSCT is indicated in CR1, and despite poorer outcomes of CR2 HSCT [30]. USP patients also waited longer for CR2 HSCT in patients at high risk of relapse. Differences in OS include death due to relapse, are therefore likely to be compounded by poorer rates and delayed timing of consolidative HSCT. Disease relapse is associated with abysmal prognosis in Brazilian centers [31], with 90% of relapsed patients dying within 3 years. Nonetheless, allogeneic HSCT rates for hematological disease in Brazil are low, and the majority of stem cell transplantation (21–100 individuals per 10 million inhabitants) are autologous. In contrast, approximately half of transplants in the UK (>500 individuals per 10 million) are allogeneic, the major indication for which is AML [32]. An important barrier is decreased availability of matched unrelated donors in Brazil compared to the UK. According to reports from the U.S.A., AML patients of Hispanic and African-Americans ancestry are less likely to receive an HSCT due to both socioeconomic factors and donor availability [33–35]. However, greater use of haploidentical donors, which have been shown to give good outcomes, should encourage greater allogeneic HSCT activity [36]. To our knowledge, this is the direct comparison between real-life outcomes for AML patients in contrasting healthcare settings. We find that the main drivers of inferior AML outcomes were higher rates of fatal infections and poorer rates of HSCT. Despite being based on retrospective data, we have performed robust statistical analysis to address potential sources of bias. However, we were unable to analyze some factors directly related to the care of the patients, e.g. length of hospital stay, time taken for presentation to hospital in emergencies, prior antibiotic exposure, occupational exposure, patient's household income, which may impact health outcomes. Nonetheless, we are confident that better results can be achieved in LMIC by implementing better patient and staff education, appropriate antimicrobial prophylaxis based on locally microbiology and susceptibility profiles, robust implementation of febrile neutropenia protocols and infection control measures to isolate and prevent spread of MDR organisms. Furthermore,

investment in infrastructure, training and alternative donor sources is needed to increase frequency and improve timeliness of HSCT.

#### Disclosure statement T

he authors have no competing financial interests to declare.

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vs matched sibling transplantation for acute myeloid leukemia in first complete remission.  
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**Table 1.** Comparative baseline characteristics.

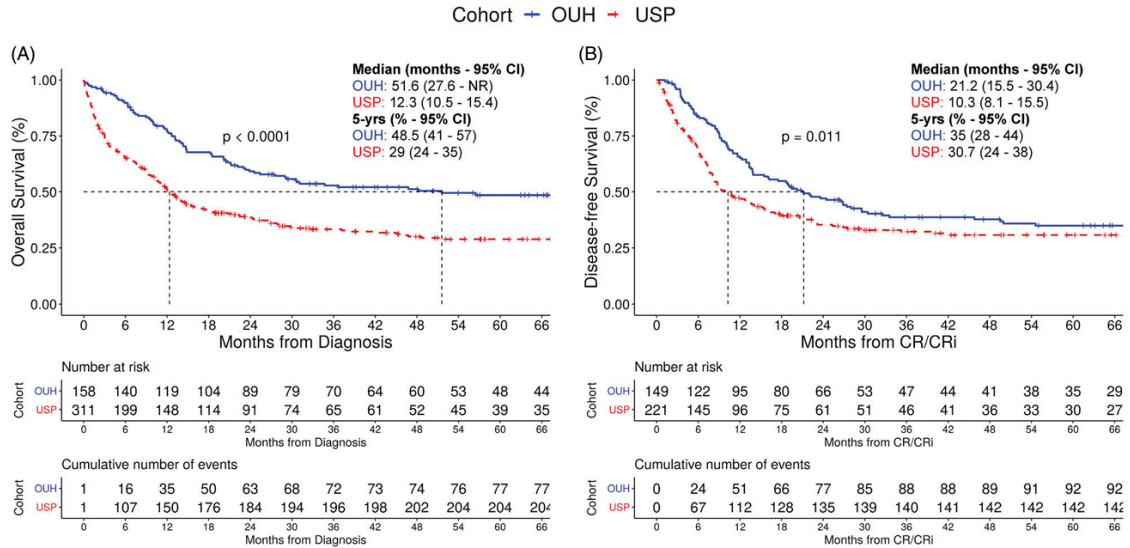
Characteristic	Median (IQR)		p Value*
	USP (N = 312)	OUH (N = 158)	
Age (years-old)	45 (31.5–56)	51.4 (42.4–59)	<.001
Serum albumin (g/dL)	3.6 (3.1–4.0)	4.1 (3.9–4.4)	<.001
WBC counts ( $\times 10^3/\text{mm}^3$ )	17.8 (3.6–53.8)	12.4 (6.9–24.6)	.14
Hemoglobin (g/dL)	8.0 (6.6–9.2)	10.2 (8.4–12.1)	<.001
PLT counts ( $\times 10^3/\text{mm}^3$ )	45.0 (24.0–87.0)	91.0 (52.5–211.5)	<.001
BM blast (%)	64 (41–84)	55 (38–80)	.13
LDH, normalized ratio	1.7 (1.0–3.0)	1.6 (1.0–3.0)	.92
No. (%)			
Sex			
Female	170 (54%)	68 (43%)	.02
Male	142 (46%)	90 (57%)	
Diagnosis			
<i>De novo</i> AML	298 (95%)	138 (88%)	.002
Secondary	14 (5%)	20 (12%)	
Adapted genetic risk (AGR)			
Favorable	92 (29.5%)	28 (20.5%)	.08
Intermediate	143 (46%)	72 (52%)	
Adverse	70 (24.5%)	39 (27.5%)	
Missing <sup>a</sup>	7 (–)	19 (–)	
Induction therapy <sup>b</sup>			
Anthracycline-based	296 (95%)	147 (96%)	.81
Other	15 (5%)	6 (4%)	
Allogeneic HSCT			
No	194 (72%)	39 (25%)	<.001
Yes	76 (28%)	118 (75%)	
CR1	42 (55%)	88 (74.5%)	
CR2	34 (45%)	30 (25.5%)	
Donor			
MRD	61 (80%)	60 (54%)	.001
MUD	9 (12%)	31 (28%)	
Haploidentical	6 (8%)	19 (18%)	

IQR: interquartile range; WBC: white blood cell; HGB: hemoglobin; PLT: platelets; BM: bone marrow; LDH: lactic dehydrogenase; USL: upper superior limit; AML: acute myeloid leukemia; HSCT: hematopoietic stem-cell transplantation; CR1: 1st complete response; CR2: 2nd complete response; MRD: matched related donor; MUD: matched unrelated donor.

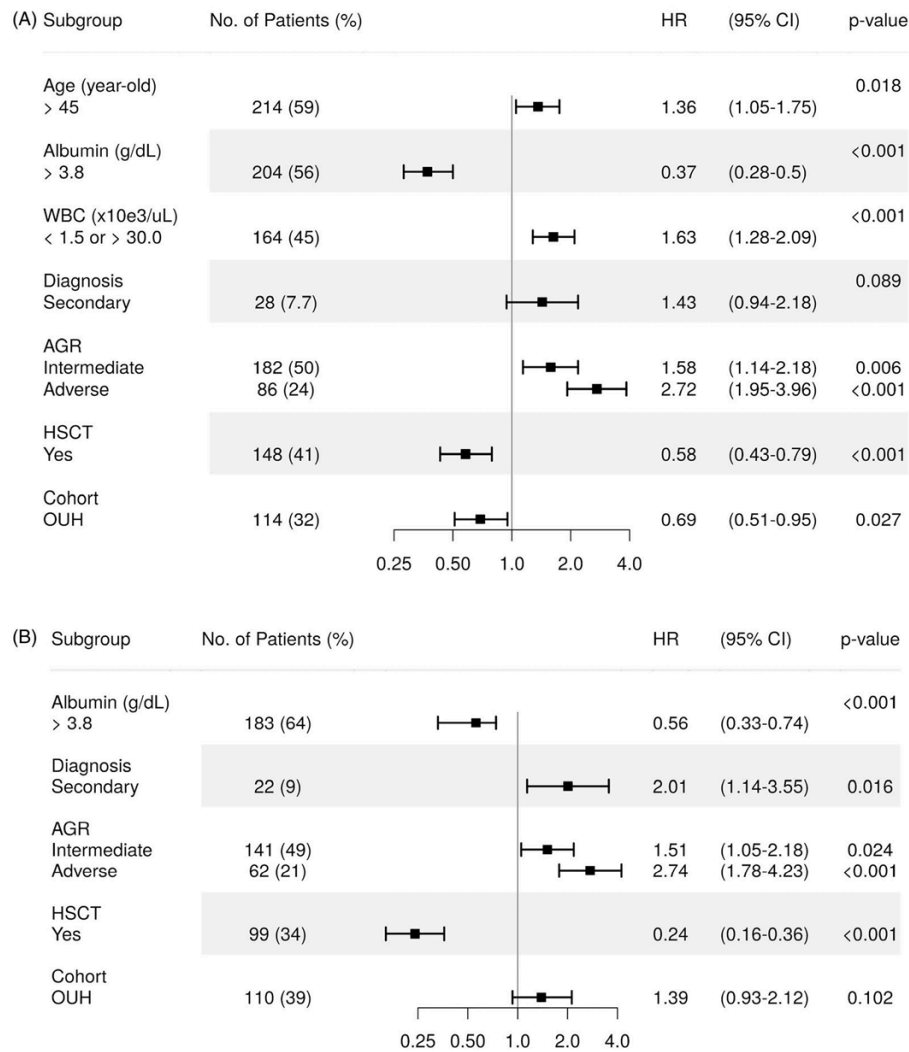
\*p Value: Wilcoxon's rank-sum and Chi-square/Fisher's tests for inter-cohorts comparisons.

<sup>a</sup>Missing data are neither being considered for groups proportions nor for p value calculation.

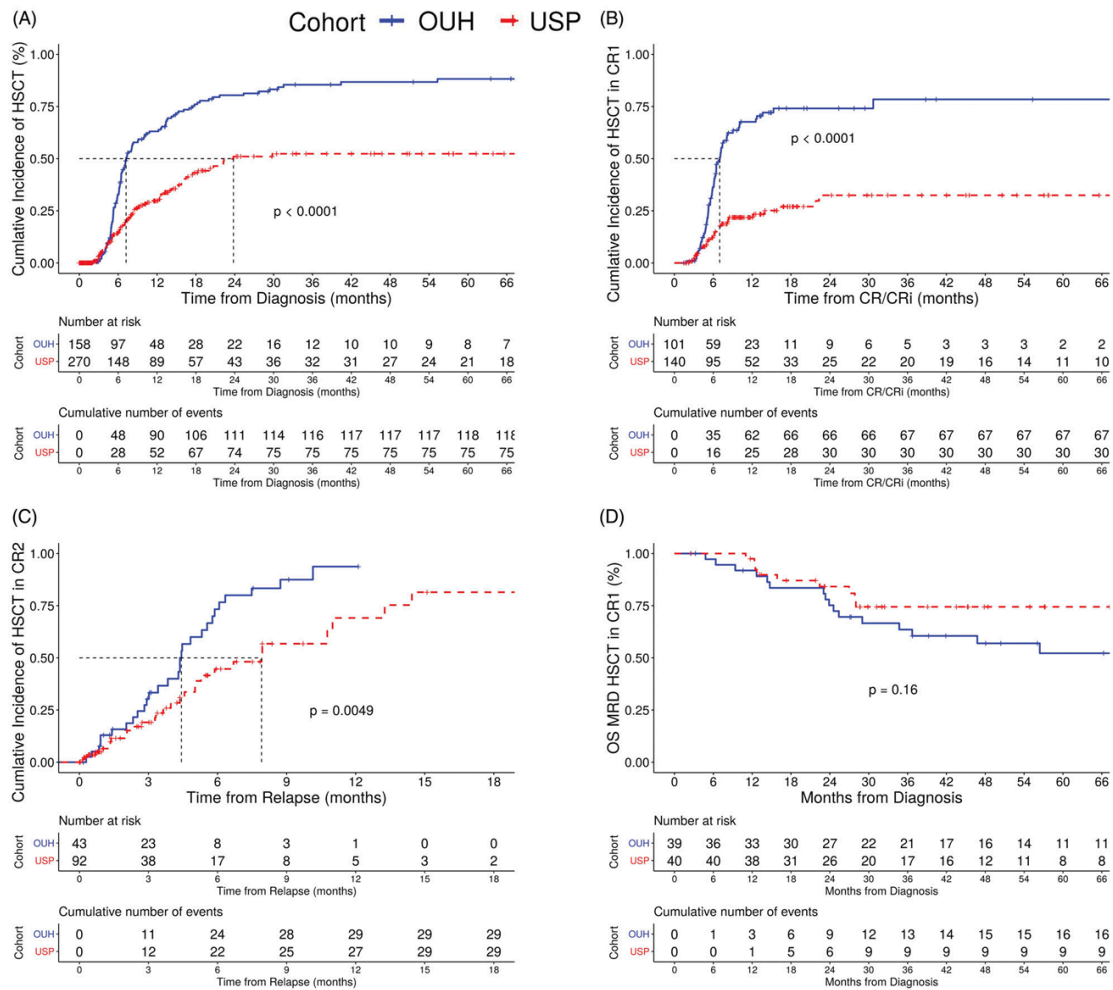
<sup>b</sup>Anthracycline-based: any regimen containing anthracycline in combination with other agents. Other: regimens not containing anthracycline in their composition (Supplementary Results Table 2).



**Figure 1.** Survival curves as estimated per Kaplan-Meier's method. (A) Overall survival for USP (dashed curve) and OUH (continuous curve); (B) disease-free survival for USP (dashed curve) and OUH (continuous curve). The vertical dashed line depicts the median.



**Figure 2.** Multivariate Cox proportional-hazard model (CPHM) having HSCT as a time-dependent variable. (A) Overall survival; (B) disease-free survival. HR: hazard ratio; CI: confidence interval; WBC: white blood cell; AGR: adapted genetic risk; HSCT: hematopoietic stem-cell transplantation.



**Figure 3.** (A–C) Cumulative incidence of hematopoietic stem-cell transplantation for USP (dashed curve) and OUH (continuous curve). (A) HSCT general, HSCT event time from diagnosis for all patients; (B) HSCT in CR1 for IR or AR AML patients, HSCT event time from CR/CR1 date; (C) HSCT in CR2 for patients who achieve a CR2, HSCT event time from relapse date. (D) Overall survival MRD HSCT in CR1. The vertical dashed line depicts the median.

**Table 2.** Comparative response and early mortality rates.

Outcome	No. (rate %)		<i>p</i> Value*
	USP (N = 312)	OUH (N = 158)	
Response			
CR/CRi <sup>a</sup>	230 (77%)	149 (94%)	<.001
Induction death	58 (19%)	5 (3%)	
Resistant disease	9 (4%)	4 (3%)	
Early mortality			
Yes	67 (23%)	9 (6%)	<.001
No	230 (77%)	149 (94%)	
EM cause			
Infection	51 (77%)	2 (22%)	.003
Bleeding	5 (7.5%)	3 (33%)	
Toxicity	1 (1.5%)	0 (–)	
Refractory	9 (14%)	4 (45%)	
Missing <sup>b</sup>	1 (–)	0 (–)	
EM infection etiology <sup>c</sup>			
GNB	28 (62%)	1 (50%)	–
GPB	5 (11%)	1 (50%)	
Fungal	12 (27%)	0 (–)	
Missing <sup>b</sup>	6 (–)	0 (–)	

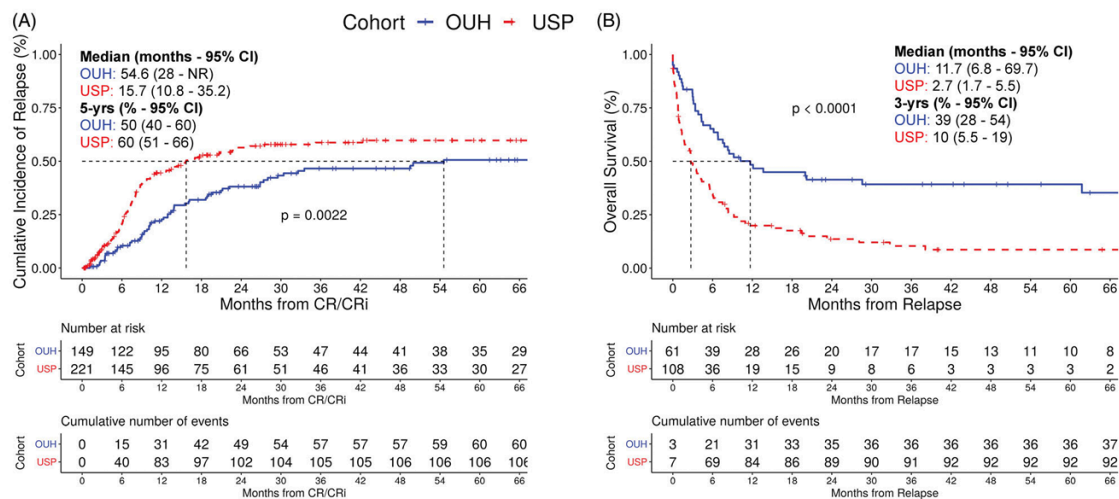
CR/CRi: complete response and complete response with incomplete hematologic recovery; EM: early mortality; GNB: Gram-negative bacteria; GPB: Gram-positive bacteria.

\**p* Value: the Kruskal–Wallis and Chi-square/Fisher's tests for inter-cohorts comparisons.

<sup>a</sup>The CR/CRi rates when removing the induction death cases were 96% and 97% for USP and OUH, respectively.

<sup>b</sup>Missing data are neither being considered for groups proportions nor for *p* value calculation.

<sup>c</sup>In USP: (1) GNB – 22 cases (78.5%) had multidrug resistant (MDR) species: 19 cases (86.4%) isolated in blood cultures: (*Klebsiella pneumoniae* in eight (43%); *Pseudomonas aeruginosa* in seven (37%); *E. coli* in two (10%); *Serratia marcescens* in one (5%); *Acinetobacter baumannii* in one (5%)); three cases (13.6%) isolated in tracheal aspirate: all *Acinetobacter baumannii*. (2) GPB – four cases (80%) of Vancomycin-resistant Enterococcus in blood cultures and one case (20%) of MRSA catheter related infection. (3) Fungal – 50% *Aspergillus sp.* (one case (16.7%) with disseminated aspergillosis isolated in blood culture, five cases (83.3%) with pulmonary aspergillosis confirmed radiologically and with galactomannan positivity); 33% *Candida sp.* (all four cases isolated in blood culture); 17% *Fusarium sp* (all two cases isolated in blood culture).



**Figure 4.** (A) Cumulative incidence of relapse for USP (dashed curve) and OUH (continuous curve); (B) survival curves as estimated per Kaplan–Meier’s method for post-relapse overall survival for USP (dashed curve) and OUH (continuous curve). The vertical dashed line depicts the median.