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Morbidity and Mortality are Not Improved by Preemptive ICU Transfer of Acute Myeloid Leukemia Patients Presenting a High Risk of Early Complications

Herve H[1,2], Lucas M[1,2], Mathieu J[1,2], Matthieu B[1,3], Clément S[1,2], Denis D[1,2] and Jean D[1,2]

[1]Service de Medicine Intensive Reanimation, Hospital Archet 1, Université Nice Sophia-Antipolis, France

[2]Équipe 2 CARRES, UR2CA - Unite de Recherche Clinique Côte d'Azur, Université Côte d'Azur, France

[3]Service de Maladies Infectiousness Infectious Diseases unit, Hospital Archet 1, Université Nice Sophia-Antipolis, France

***Corresponding author:**

Hyvernat Herve,
Service de Medicine Intensive Reanimation,
Hospital Archet 1, BP 3079, 06202 Nice cedex 3,
France

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Keywords:

Acute myeloid leukemia; HReC

Abbreviations:

AML: Acute myeloid leukemia; CNIL: French Informatics and Liberty Commission; FAB: French-American-British; HReC: High Risk of early Complications; ICD: International Classification of Diseases; ICU: Intensive care unit; KDIGO: Kidney Disease: Improving Global Outcome; LASSO: Least Absolute Shrinkage and Selection Operation; LST: Life-Sustaining Treatment; RRTs: Renal Replacement Therapies; SOFA: Sequential Organ Failure Assessment; SAPS: Simplified Acute Physiology Score; UO: Urine output

1. Abstract

1.1. Background: Acute myeloid leukemia (AML) is associated with a high rate of life-threatening early complications. Patients presenting with hyperleukocytosis >50x10⁹/L and/or promyelocytic leukemia at the time of AML diagnosis can be considered at high risk of early complications (HReC) and thus at high risk of mortality. At our institution, we propose preemptive ICU admission to HReC patients. In so doing, our goal is to prevent complication occurrence, or, failing that, to provide rapid life-sustaining treatment (LST). In the present retrospective study, we sought to determine whether preemptive ICU admission improves survival for patients newly diagnosed with AML.

1.2. Results: We analyzed a total study population of 634 patients within a ten-year period. Of that population, 24.7% (n=157) was admitted to the ICU, 20.5% (n=130) due to complications and 4.2% (n=27) preemptively. Delays to ICU admission were 12.9 hours, 7 days and 181 days for respectively the preemptive, early complications and late complications groups, p<0.001. The preemptive group showed significantly better survival at one month post ICU admission (66.7%) compared to the early (37.7%) and late (46.4%) complications groups, p=0.039. Furthermore, LST recourse in the ICU was significantly lower in the preemptive group (41% (n=11)) compared to the early (73% (n=56)) and late (73% (n=41)) complications groups, p<0.001. However, when considering survival at one-month post AML diagnosis, no significant differences were observed between patients admitted preemptively and those admitted following complications. Additionally, Cox regression identified preemptive ICU admission as a predictive factor for mortality at one month post AML diagnosis (hazard ratio 2.72, p<0.013). These contradictory data may be explained by selection and chronological biases when the analysis is limited to only ICU patients.

1.3. Conclusion: Preemptive ICU admission does not improve survival for patients with AML. Suggested benefits for preemptive ICU admission may reflect analysis biases.

2. Background

Acute myeloid leukemias (AML) are hematologic malignancies characterized by myeloblast proliferation and myeloid differentiation blockade. Although progress has been made over the past 30 years for the treatment of adult AML, its prognosis remains nonetheless predominantly poor. Life threatening complications

are frequent in the malignancy, resulting from those revealing the pathology (leukostasis, disseminated intravascular coagulation) or appearing secondarily to chemotherapy-induced aplasia (tumor lysis syndrome or sepsis). In the literature, early admissions to the intensive care unit (ICU) for AML cases varies from 9 to 28%, illustrating the disparity of admissions criteria across institutions [1-3]. Indeed, AML incidence increases with age and the states of some patients make them unable to undergo trying induction chemotherapies and even more so benefit from ICU admission.

The "golden hour" concept developed in severe trauma has expanded out to numerous other pathologies. For example, the guidelines of the Surviving Sepsis Campaign underline the need for rapid antibiotic therapy and restoration of tissue perfusion in septic shock [4]. A recent meta-analysis suggested that early admission at the start of organ dysfunction, as opposed to delayed admission obligated by the need for life-sustaining treatment (LST), lowers ICU mortality generally and especially for critically-ill cancer patients [5, 6].

At AML diagnosis, the presence of hyperleukocytosis and severe coagulation disorders identifies patients with high risks of early complications (HReC). Indeed, hyperleukocytic leukemias (leukocyte (or blast) count >100,000/L) are associated with an estimated 20 to 40% risk of early death [7-9], and coagulation disorders, particularly in promyelocytic leukemia, present significant risks for fatal hemorrhagic complications [10]. Numerous studies have shown that the appearance of a complication obligating transfer to the ICU is prognostically deleterious in hemopathies [2]. Preemptive admission involves admitting to the ICU patients who present early complication risk factors within the first hours of acute leukemia diagnosis with the goal of preventing complications via increased clinical and laboratory monitoring or providing very rapid support should organ dysfunction occur. Although interesting in principle, few clinical studies have explored this still-controversial approach [11, 12].

At the University Hospital Center of Nice (France), our ICU team has been working closely with the hematology department for many years now. Over the past ten years, the number of preemptive admissions for HReC AML cases has grown and brought with it challenges concerning the use of limited resources. We present here a retrospective analysis of these practices. Our objective for this work was to assess the ability of preemptive ICU admission to reduce early complications and improve the prognoses of patients with AML.

3. Methods

The present single-center (University Hospital Center of Nice, France) retrospective study considers the ten-year period starting on 1 January 2011 and ending 31 December 2020, this latter chosen because of the COVID-19 pandemic. The following ICD-10 codes were searched in the center's database (Clinicom software): C92.0 (acute myeloblastic leukemia), C92.2 (atypical chronic myeloid leukemia), C92.3 (myeloid sarcoma), C92.4 (acute promyelocytic leukemia), C92.5 (acute myelomonocytic leukemia), C92.6 (acute myeloid leukemia with 11q23-abnormality), C92.7 (other myeloid leukemia), C92.8 (acute myeloid leukemia with multilineage dysplasia), C92.9 (myeloid leukemia, unspecified), C93.0 (acute monoblastic/monocytic leukemia), C94.7 (other specified leukemias), C95.0 (acute leukemia of unspecified cell type), C95.7 (other leukemia of unspecified cell type), C95.9 (leukemia, unspecified). Search results involving coding errors (erroneous diagnoses, chronic myeloid leukemia, acute lymphocytic leukemia), diagnoses predating the study period, patients lost to follow-up and patients aged less than 18 years at diagnosis were excluded.

The disease start date was that of the bone marrow biopsy confirming the diagnosis or, if absent, that of the detection of peripheral blood blasts greater than 10%.

"Early" defines here the first hospitalization following AML diagnosis and any complications occurring therein (before the date of discharge). "Late" describes hospitalizations and complications occurring after the first hospitalization.

Patients were assigned to the HReC group when they presented hyperleukocytosis ≥50x10⁹/L and/or disseminated intravascular coagulation (DIC) score ≥5 points [8–10, 13, 14].

AML cases were defined as presenting complications when one or more extra-hematological organ dysfunction were detected (tachypnea >30 cycles/min, PaO2 >60 mmHg or spO2 >90% in ambient air, persistent arterial hypotension (mean <65mmHg) or need for vasopressors, acute renal failure KDIGO >2, Glasgow score <12), some necessitating LSTs like vasopressors, noninvasive (NIV), high flow oxygen therapy, invasive ventilation, renal replacement therapies (RRTs) or when complex therapeutic interventions (surgery, endoscopy, interventional radiology) were needed [4]. The development of an early complication was considered a theoretical indication for ICU admission.

Preemptive ICU admission was defined as ICU admission within the 24-hour window encompassing the AML diagnosis with no complications present, as previously described [11, 12]. The preemptive admission criteria, decided upon by consensus among the hematology and intensive care team, included patients with hyperleukocytosis (≥50x10⁹/L) and/or suspicion of acute promyelocytic leukemia (APL) based on laboratory results indicating the presence of severe coagulation disorders (DIC score ≥5 points).

At preemptive admission, the care protocol included the maintenance of platelets at >20x109/L in the absence of signs of bleeding and at >50x109/L in their presence [15], and fibrinogen levels at >1 g/L. For APL cases, the platelets threshold was set at 30x109/L and the fibrinogen level at >1.5 g/L [10]. Coagulation disorders were treated by the administration of platelet concentrate, fibrin-

ogen concentrate or fresh frozen plasma. Cytoreduction with hydroxyurea (50 mg/kg daily) was performed, accompanied by dexamethasone (10 mg every 12 hours until neutropenia) corticosteroid therapy in the presence of hyperleukocytosis ≥50x109/L.

Specific hematological therapeutics were schematized into four categories: induction chemotherapy (usually cytarabine in continuous infusion for seven days associated with an anthracycline (daunorubicin or idarubicin) for three days); hypomethylating agents (azacitidine and decitabine); palliative treatment (corticosteroid therapy, transfusions of blood products, isolated hydroxyurea administration); or early death when occurring before any initiation of therapy.

3.1. Baseline Assessment and Data Collection

The following data were collected for all patients diagnosed with AML: age; sex; Charlson score [16]; leukocyte, platelet and lactate dehydrogenase (LDH) levels; FAB classification of AML subtype; cytogenetic/molecular prognosis according to the ELN 2017 recommendations [17]; and therapeutic strategy.

Furthermore, the following data were collected for patients admitted to the ICU: leukocyte, platelet, LDH, creatinine and hematocrit levels; and SOFA [18] and SAPS II [19] severity scores for the first 24 hours. The various intensive care techniques (vasopressors, invasive or noninvasive ventilation, RRTs) and causes of death in the ICU were also noted.

3.2. Statistical Analysis

Statistical analyses were performed with pvalue.io, a graphic user interface to the R statistical analysis software for scientific medical publications (Medistica, 2021, available at https://www.pvalue.io/fr). Statistical significance was set at $p < 0.05$.

Continuous variables were expressed as medians and inter-quartile ranges (IQR). Categorical variables were reported as percentages and numbers. Continuous variables were compared between groups with the Kruskal-Wallis test and categorical variables with the chi-square test or Fisher's exact test.

Survival was analyzed with one-year Kaplan-Meier curves and compared with the log-rank test at 30 days, six months and one year.

Survival in the preemptive group was compared via three analytical models:

Model A: Survival in three subgroups admitted to the ICU: for early complications; for late complications; preemptively. This model corresponds to that used in earlier publications [18].

Model B: Survival in three subgroups of the total hospitalized AML population: patients never admitted to the ICU; patients admitted to the ICU for complications; patients admitted to the ICU preemptively.

Model C: Survival in three subgroups according to HReC risk: patients without HReC; patients with HReC; patients admitted to the ICU preemptively. This model corresponds to that used in recent publication of Desprez and al. [20].

Survival analysis was performed using a Cox model, with survival at one month, six months and one year as the outcome variables, and type of admission, age, Charlson score, HReC and leukocytes count as the explanatory variables. The candidate covariates were selected from the set of collected variables in such a way as to ensure that there were less than 20% of patients with missing data or less than 5% of variables with missing values. The candidate covariates were included in a least absolute shrinkage and selection operation (LASSO) penalized regression model. The penalty coefficient (lambda) was chosen to provide an estimation error lower than one standard deviation of the minimum error obtained by 10-fold cross-validation, while being as parsimonious as possible. No variable had a coefficient different from 0 with this lambda coefficient.

3.3. Judgement Criteria

The primary and secondary judgement criteria were respectively improved survival in the preemptive ICU admission group and reduced recourse to LST resulting from preemptive ICU admission.

3.4. Ethics Approval

The study was approved by the Société de Réanimation de Langue Française Ethics Committee (n° CE SRLF 22-017).

3.5. Accordance with Guidelines and Regulations

His study did not require individual patient consent because it involved research on a previously approved database by the French Informatics and Liberty Commission (CNIL) in accordance with French legislation on non-interventional studies.

4. Results

Mining of the hospital database identified 16,116 hospitalizations corresponding to 929 patients, 295 of whom were excluded for diverse reasons (Figure 1), leaving a total study population of 634 patients. Of this population, 24.7% (n=157) was admitted to the ICU, 20.5% (n=130) due to complications and 4.2% (n=27) preemptively. Concerning the complication-associated ICU admissions, 58% (n=77) and 42% (n=56) presented early and late complications respectively (2 patients in early admission and 1 patient in preemptive admission were hospitalized a second time for late complications).

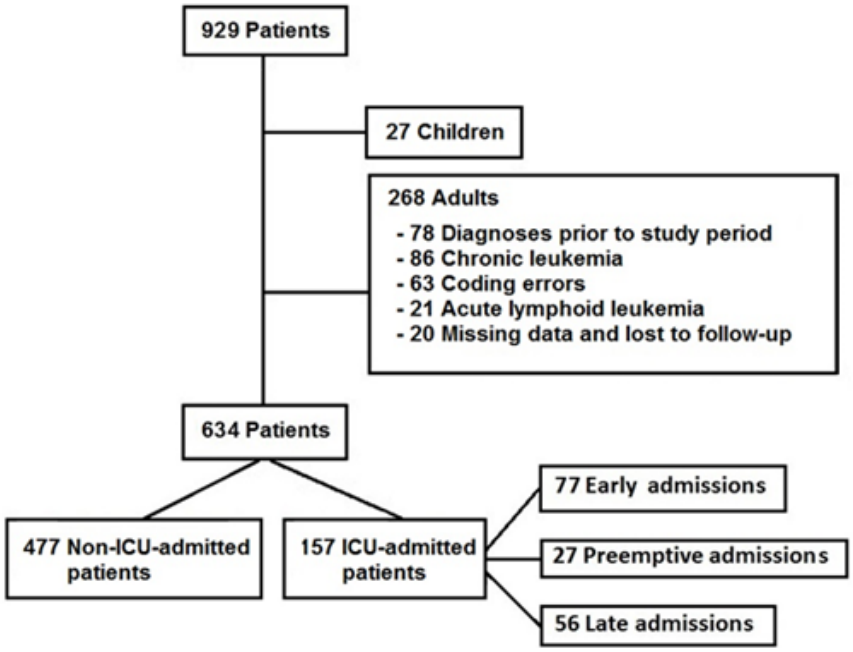

Figure 1:

4.1. ICU-Admitted Population (Table 1)

The median delay between AML diagnosis and ICU admission was 12.9 hours [IQR 0–16.9] for the preemptive, 7 days [0.8–20.4] for the early complication and 181 days [79.8–327] for the late complication groups, p<0.001. Preemptively admitted patients presented hyperleukocytosis (97.2x109/L [52.8–203]) more frequently than the early (7.9x109/L [0.3–46.7] and late (0.4x109/L [0–5.65]) complications groups did, p<0.001. Severity scores at admission were significantly different between the preemptive (SOFA: 2 points [1–5]; SAPS II: 34 points [29.5–38]), early complication (SOFA: 6.5 points [4–10]; SAPS II: 49.5 points [41.8–67.2]) and late complication (SOFA: 6.0 points [4–10]; SAPS II: 50 points [41–69.5]) groups p<0.001. LST recourse was significantly lower in the preemptive group (41% (n=11)) compared to the early (73% (n=56)) and late (73% (n=41) complications groups, p<0.001. ICU survival was significantly better for patients not requiring LST (91.3% [84.4–98.9]) compared to those requiring it (45.6% [37.2–55.8]), p<0.001.

Post ICU discharge survival was significantly better at one month for the preemptive group (66.7% [51.1–87]) compared to the early (37.7% [28.3–50.2]) and late (46.4% [36.1–74.6]) complications groups, p=0.039 (Figure 2A). However, no significant differences in survival were observed at six months or one year after ICU discharge.

Table 1: Characteristics of patients admitted to the ICU.

	Early complication %, median [IQR]	n	Late complication %, median [IQR]	n	Preemptive Admission %, median [IQR]	n	p
Age	65.1 [53.3–71.4]	77	64.8 [50–71.1]	56	58.1 [46.4–67.8]	27	0.23
Sex (M/F), %	68/32	52/25	66/34	37/19	44/56	Dec-15	0.086
Delay from diagnosis (days)	7 [0.8–20.4]	75	181 [79.8–327]	56	0.54 [0–0.705]	27	<0.001
WBC counts at diagnosis (x10^9/L)	31.1 [7.35–91.3]	71	10.7 [2.18–46.2]	44	100 [50.3–213]	27	<0.001
WBC counts at ICU admission (x10^9/L)	7.9 [0.3–46.7]	76	0.4 [0–5.65]	56	97.2 [52.8–203]	27	<0.001
Platelets ICU	29.5 [14.8–61.8]	69	22.5 [11–55.5]	56	54 [41.5–61.5]	27	<0.01
Creatinine	121 [76–214]	75	104 [61.8–162]	56	90.0 [69.5–118]	27	0.036
Hematocrit	24.0 [22–27]	76	25.8 [22.8– 29]	56	25.0 [22.5–27.5]	27	0.33
FAB AML subtype							
AML 4–5	26	20	16	9	41	11	
ALM 3	10	8	5.4	3	7.4	2	0.1

others	64	49	79	44	52	14	
Cytogenetics							
Adverse	36	28	36	21	15	4	0.079
Intermediate	23	18	36	20	48	13	0.042
Favorable	15	12	14	8	22	6	0.66
Unkown	25	19	13	7	15	4	0.13
Allograft complication	0	0	27	15	0	0	<0.001
HReC group	48	37	21	12	81	22	<0.001
SAPS2	50 [41–69.5]	77	49.5 [41.8–67.2]	56	34.0 [29.5–38]	27	<0.001
SOFA	6.5 [4–10]	77	6.0 [4–10]	62	2 [1–5]	27	<0.001
ICU techniques	73	56	73	41	41	11	<0.01
Mechanical ventilation	38	29	52	29	26	7	0.061
NIV	14	11	7.1	4	3.7	1	0.24
Vasopressors	50	38	57	32	19	5	<0.01
RRT	26	20	16	9	15	4	0.27
Length of stay ICU	2.8 [1.06–5.84]	77	2.1 [0.925–6.33]	56	4.75 [3.01–5.86]	27	0.087
DIC Score	3.0 [3.0–4.0]	77	2.0 [2.0–3.0]	56	3.0 [2.0–5.5]	27	0.01
Cause of ICU–death							
Septic shock – MOF	39	13	50	13	14	1	0.19
ARDS – MOF	24	8	27	7	14	1	
Cerebral hemorrhage	18	6	19	5	72	5	
Hemorrhagic shock	9.1	3	3.8	1	0	0	
Cardiac arrest	9.1	3	0	0	0	0	
ICU Survival	56.0% [45.8–68.59]	44	52.7% [41.0–67.8]	30	73.9% [59.0–92.6]	20	0.16
At 1 month	37.7.0% [28.3–50.2]	29	46.4% [35.0–61.5]	26	66.7% [51.1–87]	18	0.039
At 6 months	32.4% [23.5–44.8]	25	30.4% [20.4–45.1]	17	51.9% [36.1–74.6]	14	0.082
At 1 year	27.3% [18.9–39.3]	21	23.6% [14.7–38.0]	13	37.0% [22.6–60.6]	10	0.16

Abbreviations: ARDS, acute respiratory distress syndrome; HReC, high risks of early complications; ICU, intensive care unit; IQR, interquartile range; FAB, French-American-British; M/F, male/female; MOF, multiple organ failure; NIV, non-invasive ventilation; RRT, renal replacement therapy; SAPS2, simplified acute physiology score; SOFA, sequential organ failure assessment score; WBC, white blood cells.

4.2. Non-ICU-Admitted Population (Table 2)

Of the 634-patient total study population, 75.2% (n=477) was not admitted to the ICU. These patients, compared to those admitted to the ICU, had greater age (71.7 years [60.9–80.7] vs 65.1 years [52.2–71.8], p <0.001), more comorbidities (Charlson score 6 [5–7] vs 6 [4–7], p<0.001), less hyperleukocytosis (5.8x109/L [2.2–27.4] vs 24.0x109/L [2.98–71.7], p <0.001) and less frequent induction chemotherapy (47% (n=218) vs 71% (n=85), p<0.01). At the time of AML diagnosis, 8.9% (n=57) of patients who were not admitted to the ICU exhibited factors that theoretically warranted ICU admission; however, they were not transferred to the ICU. This subgroup, compared to the ICU-admitted group, was significantly older (81.2 years [72.2–85.5] vs 64.7 years [50.6–71.9], p <0.001), more affected by comorbidities (Charlson score 7 points [6–9] vs 6 points [6–9], p<0.001) and more frequently in palliative care (61% (n=31) vs 9.7% (n=7), p<0.001). Their survival, again compared to ICU-admitted patients, was lower: 24.6% [15.6–38.7] vs 46.8% [37–59.2], p<0.01, at one month; 12.3% [6.14–24.6] vs 34.2% [25.2–46.4], p<0.01 at six months; and 12.3% [6.14–24.6] vs 27.8% [19.5–39.7], p<0.01 at one year.

Survival at one month post AML diagnosis for patients not admitted to the ICU (83.4% [80.1–86.8]) was significantly better than that of the other groups, p>0.001 (Figure 2B). In this model, the survival of patients admitted preemptively was 66.7% [51.1–87.0], significantly lower than the group without ICU admission and identical to the group admitted for early complications, 67.9% [60.2–76.5]. At six months and one year post AML diagnosis, no differences between the three groups remained significant.

Table 2: Characteristics of all population with newly diagnosed ALM

	No ICU %, mediane [IQR]	n	ICU %, mediane [IQR]	n	Preemptive %, mediane [IQR]	n	p
Age (years)	71.7 [60.9 - 80.7]	477	65.1 [52.2 - 71.8]	130	58.1 [46.4 – 67.8]	27	<0.001
Sexe (M/F)	55/45	260/217	68/32	88/41	44/56	Dec-15	<0.01
WBC counts at diagnosis ($x10^9$/L)	5.8 [2.2 - 27.4]	425	24.4 [2.98 – 71.7]	116	103 [50.8 - 209]	27	<0.001
> 50 ($x10^9$/L)	15	66	31	36	74	20	<0.001
> 100 ($x10^9$/L)	5	23	17	20	52	14	<0.001
Platelets ($x10^9$/L)	53 [29 - 108]	393	51 [25.2 - 118]	102	58 [34.0 – 62.0]	25	0.92
LDH (UI/L)	618 [398 - 1061]	301	882 [508 - 1704]	78	1395 [764 - 2268]	19	<0.001
Charlson Score (Points)	6 [5 - 7]	477	6 [4 - 7]	129	4 [3 - 5.5]	27	<0.001
FAB subtype							
AML 4-5	11	52	22	28	41	11	<0.001
AML 3	5	23	8	10	7	2	0.27
Others	84	402	71	92	52	14	<0.001
Cytogenetics							
Adverse	49	232	37	48	15	4	<0.001
Intermediate	24	116	28	37	44	12	0.098
Favorable	13	61	15	19	26	7	0.27
Unknow	14	68	20	26	15	4	0.31
Theorical indication to ICU during first admission	12	57	54	68	44	12	<0.001
Risk group	19	89	35	46	81	21	<0.001
Treatment							
Induction	47	218	71	85	74	20	<0.001
Hypomethylating agents	33	154	17	20	0	0	<0.001
Palliative care	18	83	4.2	5	11	3	<0.001
Early deaths	1.5	7	7.6	9	15	4	<0.001
Allograft	26	124	23	29	22	6	0.37
Micro-allograft	0.63	3	0.78	1	3.7	1	
Survival after AML diagnosis							logrank
1 month	83.4% [80.1 - 86.8]	393	67.9% [60.2 – 76.5]	89	66.7% [51.1- 87.0]	18	<0.001
6 months	59.2% (55 - 63.8]	279	53.1% [45.1 - 62.5]	68	55.6% [39.6 -77.8]	15	0.18
1 year	44.8% (40.5 - 49.6]	210	35.7% (28.2 - 45.1]	46	36.7% [22.2 - 60.4]	10	0.07

Abbreviations: IQR, interquartile range; FAB, French-American-British; LDH, lactate deshydrogenase; M/F, male/female; WBC, white blood cells.

4.3. High Risk of Early Complications Group

HReC patients represented 26% (n=164) of the population. Subgroup distributions were 56% (n=92) of patients not admitted to the ICU, 29% (n=49) of patients admitted to the ICU for early or late complications and 14% (n=23) of patients admitted to the ICU preemptively. Four patients had high leukocytosis but did not meet the criteria for a high risk of complications. The patients in the preemptive admission group had significantly lower age (58.1 years [46.4–67.8] vs 70.3 years [51–79.3], p <0.001) and less morbidity (Charlson score 4 points [3–5.5] vs 6 points [4–7]), p<0.001. Hyperleukocytosis was more marked in the preemptive group as well (103x109/L [50.8–209] vs 69.5x109/L [44–112]), p=0.001. DIC score was higher in the HReC group (3 points [1–5] vs 2 points [1–4], p<0.001.

Early theoretical indication for ICU transfer motivated by the development of organ dysfunction was found in 42% (n=60) of HReC patients vs 41% (n=11) of preemptive admission patients, p=0.89.

One-month post AML-diagnosis survival for non-HReC patients (85.4% [82.2–88.7]) was significantly better than those for HReC

patients (65% [57.6–73.4]) and preemptive ICU admission patients (66.7% [51.1–87.0]), p<0.001 (Figure 2C). At six months and one year, no differences between the three groups remained significant. Patients admitted preemptively exhibited a comparable survival rate to HReC patients at all points, including at 4 days from the AML diagnosis (median length of preemptive ICU admission), at which point 15% (n=4) of preemptive admission patients had died compared to 18% (n=25) of HReC patients, p=non-significant.

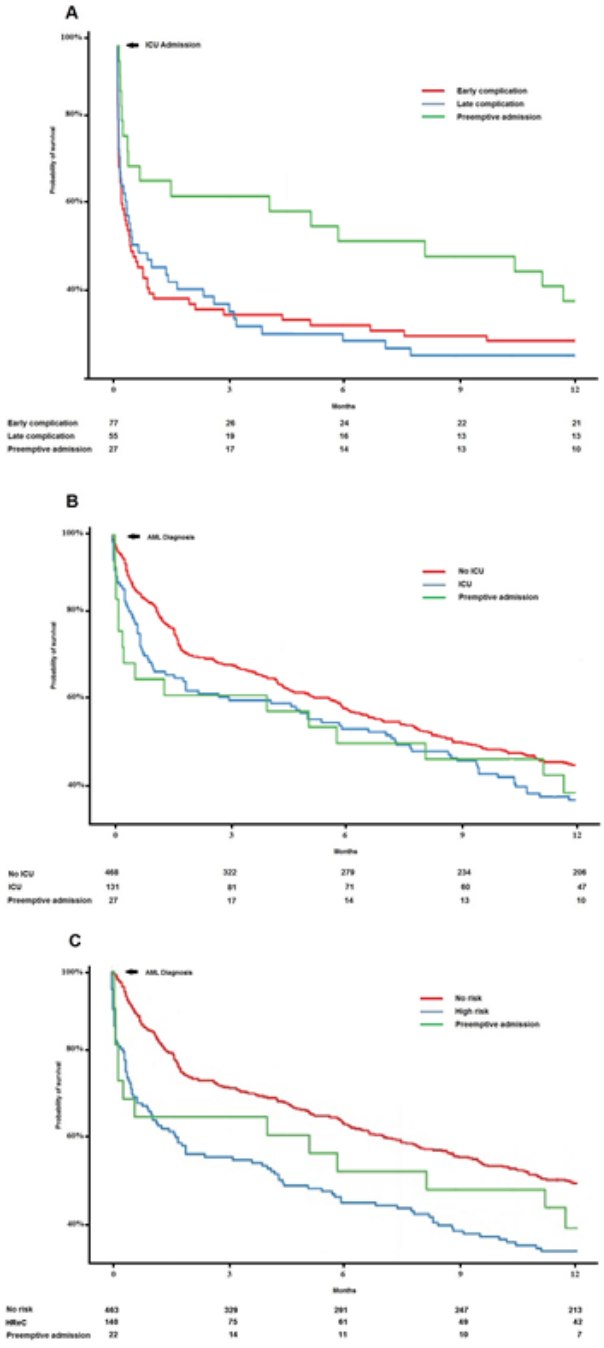

Figure 2: Kaplan-Meier curves for one-year survival. A - From ICU admission between ICU groups for early complications, late complications and preemptive admission. B - From AML diagnosis between no ICU, ICU, and preemptive groups. C – From AML diagnosis between no risk, high risk, and preemptive groups.

4.4. Factors Predictive of Mortality at AML Diagnosis (Figure 3)

Using Cox regression in the total study population (n=634), the factors predictive of post AML-diagnosis mortality were ICU admission for complications (hazard ratio (HR) 2.37, p<0.001 at 1 month; HR 1.69, p<0.01 at 6 months; HR 1.6, p<0.001 at 1 year), age (HR 1.04, p<0.001 at 1 month; HR 1.04, p<0.001 at 6 months; HR 1.034, p<0.001 at 1 year), Charlson HR 1.19, p<0.001 at 6 months; HR 1.18, p<0.001 at 1 year) and leukocytes (HR 1.04, p<0.01 at 1 month; HR 1.05, p<0.001 at six months; HR 1.05, p<0.001 at 1 year). HReC status was identified as a mortality risk factor at 1 month and 6 months (respectively HR 1.93, p<0.01 and HR 1.46, p=0.037. Against all expectations, preemptive admission to the intensive care unit was found to be a factor increasing the risk of mortality during the first month (HR 2.24, p<0.041).

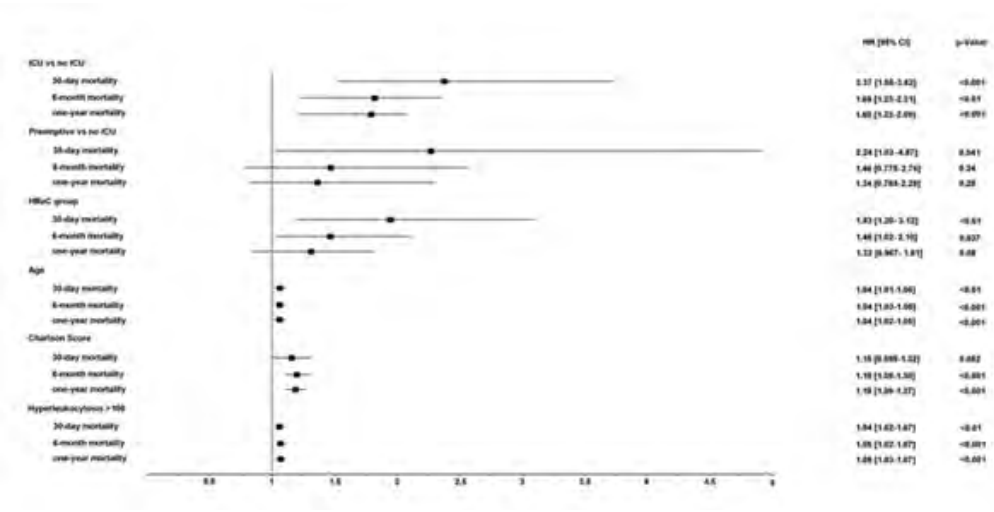

Figure 3: Factors predictive of mortality at one month, six months and one year post AML diagnosis.

5. Discussion

For patients diagnosed with AML and presenting laboratory markers of potentially life-threatening complications, preemptive ICU admission should, in principle, enable the prevention of those complications or at least improved prognosis via the rapid deployment of LSTs should they occur. In our study, preemptive admission occurred very rapidly—12.9 hours on average—and concerned mainly patients identified as having a high risk of early complications. The studies on preemptive ICU admission in the literature do not inspire great confidence. Lengliné et al reported a tendency toward improved survival with preemptive admission (ICU survival of 79% for preemptive ICU admission vs. 65% for late ICU admission, p=0.12) [11]. That team also observed less LST recourse with preemptive admission (nearly 2-fold decrease in mechanical ventilation and nearly 4-fold decrease in vasoactive drugs). Mottal et al found similar results, reporting greater use of RRT, amines and invasive ventilation in late ICU admission and reduced morbidity with preemptive admission [12]. But these studies compare survival in ICU between a preemptively admitted group and a group admitted for early complication (identic to our Model A). In this model, we too observed improved post-ICU survival at one month and significantly reduced LST recourse in preemptive ICU admission. But comparing the preemptive group to groups admitted to ICU for complications introduces an obvious bias. Indeed, we observed significant differences between the severity scores of patients admitted preemptively and those admitted following complications. Those differences could be interpreted as inherent to the selection process of the preemptive group. These patients were chosen before the development of complications and thus in better states of health; the reduced use of LSTs would logically be the result of preventive treatments warding off the development of those complications. However, that interpretation would require, in the absence of specific interventions, a probability of complications in the preemptive group close to 100%, similar to that of the group admitted for complications. It was therefore essential to know the incidence of complications in the HReC group from which the preemptive group was selected. We found that the real incidence of complications in the HReC group was 42%, which was similar to that of the preemptive group. These findings suggests that more than half of HReC patients and more than half of preemptively admitted patients will never present a complication imposing transfer to the ICU. Therefore, the potentiality of exacerbation is largely different between patients admitted to the ICU preemptively and those admitted there because of the development of complications, and any interpretations on this model will show a selection bias. Furthermore, there is a chronological bias. In patients admitted preemptively, complication development is limited to a short, median four-day window at the start of hospitalization. In patients admitted following the development of a complication, that chronological window is much wider. To take that time effect into account, it is more logical to compare survival in the whole population from the date of the AML diagnosis (Model B). Here again, in

our study, we were unable to demonstrate an improvement in survival. A best methodology is probably to compare the survival of the preemptive group to the survival of the HReC group (model C) because patients in preemptive admissions are essentially patients with risks of early complications. Recently, Desprez et al, found that preemptive admission of newly diagnosed ALM with hyperleukocytosis ≥50x109/L at diagnosis did not provide a survival benefit compared to the hematology population never admitted to the ICU [20]. Contrary to our study, the preemptive group exhibited no mortality, which is surprising for a high-risk population. Another argument in favor of preemptive admission would be the improvement of long-term prognosis by increasing the number of patients who can benefit from a full induction protocol. Our study also does not demonstrate any improvement in survival beyond the first three months and also does not appear to increase the number of patients receiving bone marrow transplants.

A possible explanation for the lack of benefit of preemptive admission is the brutality and intensity of the observed complications, despite the preventive measures deployed to avoid them. The main cause of early death is hemorrhage, usually intraparenchymal cerebral or pulmonary, that rapidly becomes uncontrollable in a setting of severe coagulation disorders [7]. Leukostasis, the phenomenon of microvascular obstruction by aggregations of circulating blasts, seems to be at the root of the problem. Leukostasis sets off complex endothelial-cell activation mechanisms involving such cytokines and inflammatory factors as IL-1β and TNF-α and promoting the expression of cell adhesion molecules like ICAM-1 and VCAM-1 [21]. Although hemorrhagic events are correlated with hyperleukocytosis, the rapid reduction of circulating blasts is not sufficient for reducing mortality. Techniques thereto like rapidly efficacious leukapheresis or slower cytoreduction with hydroxyurea have not been shown to provide a significant improvement in survival [22, 23]. It may be possible that during cytoreduction, certain patients will have accesses of inflammation, triggering endothelial activation and the resulting hemorrhage. Building upon this pathophysiological hypothesis, the use of dexamethasone has been proposed, but any benefits of it remain controversial and demonstrated only for lung injury and in only a small study population [24].

Our study is limited by its retrospective and single-center nature and by the small number of patients in the preemptive group. We did not perform a propensity score analysis in our study because we believe that the matching criteria cannot be met. The small sample size, and more importantly, the specific selection of younger, less comorbid patients receiving ICU surveillance in the preemptive group, leaves a majority of older, comorbid patients without close monitoring in the control group. Both groups will not be collinear and will not allow for achieving a balance in the covariates necessary for model validation [25]. Analyzing survival at different times can also be confusing, but it was important to select a model that had been previously used to demonstrate that identical results could be falsely obtained. The choice of a threshold at 50x109/L to define hyperleukocytosis can also be criticized as it tends to diminish the severity of the HReC group. However, that limitation should have favored the preemptive group. The results of our study may also raise questions as to the validity of deployed preventive measures, notably for the management of coagulation disorders. Having followed current treatment guidelines in our study, the results of this latter may suggest that treatment thresholds are underestimated for this subgroup with high risks of early complications. There is no consensus on hydroxyurea and dexamethasone in the AML setting, but their use is more of a question of futility than an explanation of our negative results. Only a prospective, randomized study could perhaps bring clarity to this question by discarding the selection bias. However, considering our discouraging results, doing so would surely result in a high number needed to treat and immobilize precious human and technical resources.

6. Conclusion

We were unable to establish a favorable outcome associated with preemptive ICU admission for AML patients at high risk of early complications. While targeting this population is a prudent approach due to the significant occurrence of complications, intensive care specialists continue to face limitations in managing acute myeloid leukemia effectively. In our view, to enhance the prognosis of hyperleukocytic leukemia, it may be more beneficial to prioritize a deeper comprehension of the mechanisms responsible for hemorrhagic complications related to leukostasis and the advancement of specialized hemostatic treatments, rather than placing primary emphasis on early transfer to the intensive care unit.

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