Characteristics of patients with newly diagnosed acute myeloid leukemia not receiving treatment

Acute myeloid leukemia (AML) is a heterogeneous malignancy characterized by clonal expansion of myeloid precursor cells. Advances in therapeutic strategies have improved survival in AML, including elderly unfit patients. However, patients who receive intensive therapy spend 30% or more of their life after diagnosis in a hospital compared to patients receiving less-intensive options.[1] Other investigators found that AML patients receiving lower-intensity treatment regimens devoted an average of 42% of days following their diagnosis to their oncology care.[2] Additionally, Hubscher. *et al*. reported that an average of 30% of patients in the US do not receive any anti-leukemic treatment after diagnosis.[3] Little to no studies report outcomes of these non-treated patients, especially with the relatively recent integration of molecular sequencing. This study evaluates the clinical characteristics, cytogenetic/molecular features, and survival outcomes of untreated AML patients to identify factors that may influence treatment decisions and prognosis.

After obtaining appropriate institutional review board approval, we retrospectively reviewed the charts of 429 patients newly diagnosed with AML at Mayo Clinic, Rochester, between January 2016 and January 2023, of whom we identified 40 (9%) patients who did not receive therapy following their AML diagnosis. Patients were subcategorized into primary AML, AML following a myeloid neoplasm (myelodysplastic syndrome [MDS], myeloproliferative neoplasm [MPN], MDS/MPN), and myeloid neoplasm post cytotoxic therapy (MN-pCT).[4] Patients with no cytogenetic or molecular data available were excluded from the study. Patients who previously received therapy for AML were also excluded (relapsed or refractory). The reasons for patients not receiving treatment were categorized into three main groups: (i) patient preference applied to patients who were presented with the option of treatment, whether curative or palliative, but chose to decline; (ii) medical reasons/physician recommendations referred to cases where patients' clinical status and comorbidities excluded them from receiving any form of anti-leukemia treatment; (iii) unknown reasons accounted for patients whose rationale for foregoing treatment was not documented. All data were recorded at the time of diagnostic bone marrow biopsy. Lactate dehydrogenase (LDH) was considered elevated if it was above 222 U/L. We stratified risk using the 2022 European LeukemiaNet (ELN) risk stratification.[5] Overall survival (OS) was calculated from the date of AML diagnosis to the date of last follow-up or death. Date of decision refers to the day it was determined that a patient will not receive therapy for AML. For statistical analysis, we used BlueSky Statistics V10.3.4.

Among the untreated group (N=40 [9.3%]), 60% were male. Thirty patients (75%) had an abnormal karyotype, with the most common karyotype abnormalities being complex karyotype (47.5%), monosomy 7 (17.5%), deletion 7q (12.5%), and trisomy 8 (12.5%). Targeted next-generation sequencing (NGS)[6] (Figure 1A) was performed on bone marrow samples from 26 patients, with *TP53* being the most frequent mutation (30.8%), followed by *NPM1* (25.8%), and *FLT3*-internal tandem duplication (ITD) (28.1%) (*Online Supplementary Figure S1*). In the cases of *NPM1* and *FLT3*-ITD mutations, more than half of the patients made the decision to defer therapy before the results of molecular sequencing were back. By AML ELN22 risk stratification, 25 patients (62.5%) had adverse risk, while 12 (30%) and 3 (7.5%) had intermediate and favorable risk, respectively.

Reasons for patients not receiving treatment were patient preference (N=29, 72.5%), medical reasons/physician recommendations (N=10, 25%), and unknown reasons (N=1, 2.5%) (*Online Supplementary Figure S2*). No difference in OS was found in the untreated group across the different categories of deferred therapy (Table 1). Of 40 untreated patients, 25 (62.5%) had Medicare coverage, 11 (27.5%) had no insurance coverage, and four (10%) had private insurance. Median time from diagnosis to decision of no treatment was 15 days. Twenty-four of the 40 patients (60%) were enrolled in hospice, while 16 patients (40%) pursued best supportive care (BSC) (Figure 1B). In the untreated group, 40% of patients died at home, 27.5% in a hospital, 17.5% in an inpatient hospice facility, and 15% had an unknown location. Treatment options differed based on the year of AML diagnosis. Low-dose cytarabine and hypomethylating agents (HMA) were primarily used in patients ineligible for intensive therapy. In 2018, venetoclax (VEN) was approved and added to these regimens. In fit patients, a "7+3"-based regimen was the backbone for treatment. The most common regimens in the treated group were "7+3"-based regimen (N=160, 41.1%) and HMA+VEN (N=149, 38.3%). Using the VEN approval date (November 2018) as a cutoff date, we identified 134 patients diagnosed before and 295 patients diagnosed after that date. Therapy deferral rates decreased following VEN's approval, where 17 of 134 patients (12.7%) diagnosed before approval did not receive therapy, compared to 23 of 295 patients (7.8%) diagnosed afterwards.

The median age for the untreated group was 77 years (range, 54-94) compared to 67 (range, 18-92) in the treated group (N=389) (P<0.001). Peripheral blasts were higher among the untreated group (median 29% *vs*. 20%; P=0.029). Additionally, LDH was elevated in all untreated patients who had their levels measured (N=35, 100%) compared to the

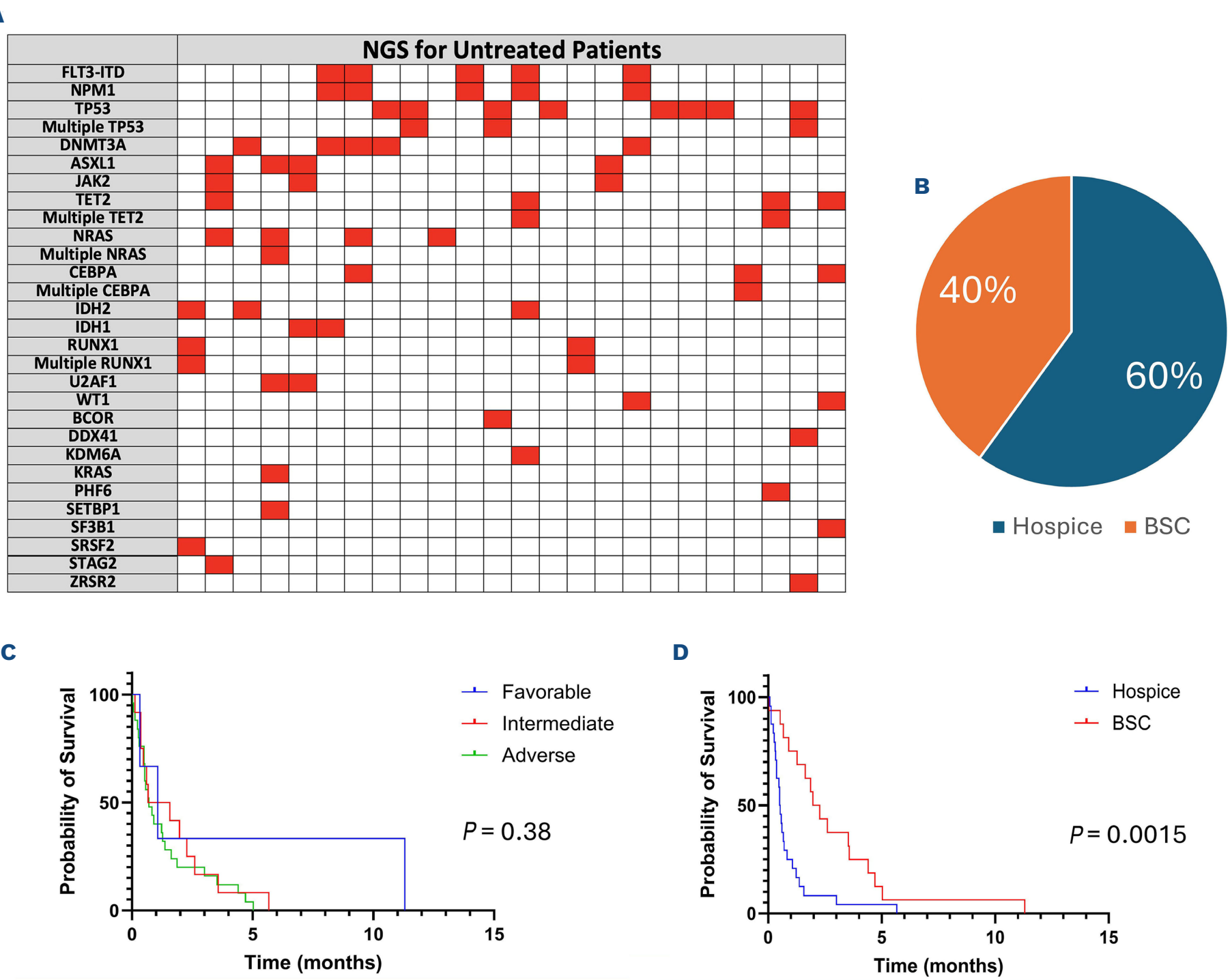

Figure 1. Untreated patients' molecular, care pattern, and survival analysis. (A) Mutational pattern of untreated patients that had undergone next-generation sequencing (NGS) analysis (each column represents a patient). (B) Untreated patients' pattern of care after acute myeloid leukemia (AML) diagnosis. (C) Overall survival according to European LeukemiaNet 2022 risk stratification in untreated patients. (D) Overall survival between hospice care and best supportive care in untreated patients. BSC: best supportive care.

treated group (N=250, 76.2%; *P*<0.001). Median WBC was higher in the untreated group (5.3 *vs*. 4.5; *P*=0.03). Myeloid neoplasm-pCT was significantly higher in the untreated group (N=20, 50% *vs*. N=99, 25.4%; *P*=0.002). Complex karyotype was also more common in untreated patients (47.5% *vs*. 30.5%; *P*=0.033). No difference in AML ELN 2022 risk stratification and mutation frequencies was seen between the two groups (*P*>0.05). Median OS was 0.8 months (range, 0.03-11.3) in the untreated group compared to 14.8 months (range, 0.2-106.4) in the treated group. ELN 2022 risk stratification did not impact OS in the untreated group (*P*=0.38) but did in the treated group (*P*<0.0001) (Figure 1C). MN-pCT did not influence OS in the untreated group (*P*>0.05), unlike in the treated group, where those patients had a significantly decreased median OS (7.9 *vs*. 20.3 months; *P*<0.0001). Among the untreated group, neither karyotype abnormalities nor mutations influenced OS (*P*>0.05), unlike in the treated group, where the existence of complex karyotype, monosomy 7, *FLT3*-ITD, *NPM1*, and *TP53* mutations significantly decreased OS (*P*<0.05) (*Online Supplementary Figure S3*). While LDH, alanine amino-transferase (AST), aspartame amino-transferase (ALT), bilirubin s and creatinine serum levels did not affect the OS within the untreated group, normal glucose levels were associated with increased median OS compared to elevated glucose levels (1.3 *vs*. 0.4 months; *P*=0.0004). Within untreated patients, median OS in patients pursuing BSC was longer compared to patients in hospice care (2.1 *vs*. 0.5 months; *P*=0.0015) (Figure 1D).

Different studies have identified the low rate of hospice

Table 1. Treated and untreated patient characteristics.

Variables	Untreated N=40	Treated N=389	*P*
Age at diagnosis, years, median (range)	77 (54-94)	67 (18-92)	<0.001
Sex: male, N (%)	24 (60)	228 (58.6)	1
ELN2022 AML risk profile, N (%)	Favorable: 3 (7.5) Intermediate: 12 (30) Adverse: 25 (62.5)	Favorable: 71 (18.3) Intermediate: 92 (23.7) Adverse: 226 (58.1)	0.207
Diagnosis, N (%)	AML following a myeloid neoplasm: 11 (27.5) Primary: 29 (72.5)	AML following a myeloid neoplasm: 110 (28.3) Primary: 279 (71.7)	1
Myeloid neoplasm-pCT, N (%)	20 (50)	99 (25.4)	0.002
WBC x10^9/L, median (Q1-Q3)	5.3 (2.3-53.6)	4.5 (2.0-17.4)	0.033
Peripheral blasts %, median (Q1-Q3)	29 (10-72.5)	20.0 (5-50)	0.029
LDH U/L, median (Q1-Q3)	383 (273-594.5)	351.5 (224.8-590.8)	0.562
LDH, N (%)	Elevated: 35 (100) Not elevated: 0 (0)	Elevated: 250 (76.2) Not elevated: 78 (23.8)	<0.001
Karyotype, N (%) Abnormal Complex Monosomy 7 Deletion 7q Trisomy 8	 30 (75) 19 (47.5) 7 (17.5) 5 (12.5) 5 (12.5)	 253 (66.1) 117 (30.5) 58(15.1) 35 (9.1) 52 (13.6)	 0.293 0.033 0.649 0.566 1
Median overall survival, months	0.8	14.8	<0.0001
Mutations, N (%) NGS *TP53* *FLT3*-ITD *NPM1*	 26 (65) 8 (30.8) 9 (28.1) 8 (25.8)	 350 (90) 77 (21.9) 55 (15.1) 54 (14.9)	 <0.001 0.33 0.075 0.123

AML: acute myeloid leukemia; ELN: European LeukemiaNet; WBC: white blood count; LDH: lactate dehydrogenase; NGS: next-generation sequencing; pCT: post cytotoxic therapy; ITD: internal tandem duplication.

service use in patients with AML.[7,8] Moreover, LeBlanc *et al*.[9] found that patients with acute leukemia who were transfusion dependent prior to enrollment in hospice care had a shorter hospice length of stay compared to patients who were not, indicating that hospice services did not meet patients' needs and that patients experienced a barrier to timely referral. In our study, untreated patients who pursued BSC had an increased median OS compared to patients who received hospice care. It is important to mention that as more drugs are getting approved in AML, especially for targetable mutations such as *NPM1* and *FLT3*, awaiting the results of work-up and expediting such results may have an impact on decision making. Limitations to this study include single-institution experience, the relatively small number of patients analyzed, and the retrospective design of the study. Additionally, this study was done at a large academic center, which may not represent a common real-world experience, and it could under-represent the "untreated" population.

In conclusion, patient preference was the most common reason for deferring therapy at the time of AML diagnosis. This may have been impacted by multiple factors like older age and more frequent high-risk AML (complex karyotype, mutated *TP53*, and MN-pCT) in the untreated group. Albeit short, the OS in untreated patients pursuing BSC was significantly higher than in patients enrolled in hospice care. As more suitable less intensive and targeted therapies get approved, the frequency of patients deferring therapy at diagnosis may decrease in the future.

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Disclosures

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Contributions

OA and AA-K designed the project, reviewed the data, and wrote the manuscript. OA and YJ performed statistical analysis. YJ, RH, DV, KB, PG, DJ, JMF, TB, CAY, YK, ANS, MHT, AM, WJH, AM, HA, MP, MS, KB, and MRL reviewed the manuscript.

Data-sharing statement

For original data, please contact the corresponding author.

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