INTRODUCTION

T-cell acute lymphoblastic leukemia (ALL)/lymphoma is an uncommon disease in adults and more aggressive than the more common pediatric counterpart. T-ALL in adults, however, is potentially curable with 50% of 5-year survival rate. Chromosomal translocations occur in a subset T-ALL cases; these translocations often involve the T-cell receptor gene loci or KMT2A with variable partner genes, including TAL1, TAL2, TLX1, TLX3, HOXA, LMO1, LMO2, and NKX2. Several genes involving various cellular signaling pathways have been identified as potential therapeutic targets.
pathways are also recurrently mutated in T-ALL. Examples of these mutations are PTEN mutation/deletion in PI3K-AKT pathway and N/KRAS mutations in MAPK-ERK signaling pathway. Activation of NOTCH1 pathway is also a hallmark of both pediatric and adult T-ALL implicating a favorable outcome.\(^{11-13}\) In most instances NOTCH1 activation results from activating mutations in NOTCH1 but in fewer cases loss-of-function mutations in FBXW7, an inhibitor of NOTCH1, lead to constitutive NOTCH1 overexpression.\(^{14,15}\) Various combinations of common gene alterations in T-ALL have been associated with different responses to therapy and different clinical outcomes.\(^{8,16-19}\)

The overall outcome in adult T-ALL has improved over the past several decades, largely due to better risk stratification and intensified chemotherapy regimens.\(^{20-22}\) Major prognostically important clinical factors in T-ALL patient are age at diagnosis, peripheral blood (PB) count (tumor burden), maturational stage of neoplastic cells and CNS involvement.\(^{2,23}\) Status of minimal residual disease (MRD) is considered the single most influential factor in predicting long-term survival after induction therapy.\(^{24-28}\)

Several large scale studies have shown clinically relevant genetic changes in both pediatric and adult T-ALL.\(^{9,11,18,19,29-31}\) Trinquand et al suggested that a NOTCH1/FBXW7/RAS/PTEN-based classifier predicts relapse-free survival (RFS) and overall survival (OS) in adults with T-ALL.\(^{29}\) The utility of this approach was further confirmed in children with T-ALL.\(^{32,33}\) In this model, T-ALL with mutations in NOTCH1/FBXW7 (N/F) without any changes in either (K/N) RAS or PTEN (R/P) is considered a genetically low-risk group, whereas all other combinations of these gene mutations were considered genetically high-risk.\(^{29}\) The induction chemotherapeutic regimen used in previous studies for this oncogenic classifier consisted of vincristine, daunorubicin, L-asparaginase, and cyclophosphamide (Berlin-Frankfurt-Münster [BFM] protocol).\(^{29,33}\) The standard treatment regimen for adults with T-ALL at our institution, however, is hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD) with or without nelarabine (https://clinicaltrials.gov/ct2/show/NCT00501826).\(^{34}\) The reproducibility of (N/F/R/P) risk stratification model in adult T-ALL patients treated with hyper-CVAD ± nelarabine has not been evaluated. In this study, we assessed the applicability of this model in our cohort of adults with T-ALL treated with hyper-CVAD ± nelarabine.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

We searched the electronic medical record to identify adult patients with T-ALL in the bone marrow (BM) between 2012 and 2018. Inclusion criteria included: (a) patients ≥18 years; (b) those who were treatment-naïve at time of first presentation to our institution; (c) patients treated with hyper-CVAD ± nelarabine; and (d) next-generation sequencing (NGS)-based mutation analysis was performed. Exclusion criteria included: (a) blast crisis of chronic myeloid leukemia with T-lymphoblasts; (b) mixed phenotype acute leukemia; (c) patients with nodal or extranodal involvement by T-lymphoblastic lymphoma with minimal (≤5% blasts) BM involvement.

The clinicopathologic, cytogenetic and mutational data on patients in the study were collected by reviewing patients’ electronic medical records. Complete remission (CR) or CR with incomplete hematologic recovery (CRi) were assessed according to the latest national comprehensive cancer network clinical practice guidelines.\(^{35}\) Qualitative polymerase chain reaction-based methods were performed using genomic DNA (gDNA) extracted from BM aspirate specimens to assess for rearrangements of TRG and TRB.\(^{36}\) Measurable MRD was analyzed by multiparameter flow cytometry (MFC) analyses (assay has been validated to a sensitivity of 0.1%-0.01%). This study was approved by the institutional Review Board at The University of Texas MD Anderson Cancer Center and performed in accord with the Declaration of Helsinki.

### 2.2 | NGS analysis

Next-generation sequencing-based mutation analysis was performed using previously described 28-gene or 81-gene panels (complete list of the genes in Table S1).\(^{37}\) Briefly, sequencing libraries were prepared from 250 ng of gDNA using HaloPlex Target Enrichment Kit (Agilent Technologies) and sequencing libraries were subject to a MiSeq sequencer (Illumina). NGS data analysis was performed using SureCall (Haloplex). The Integrative Genomics Viewer (IGV; Broad Institute) was used to visualize read alignment and confirm variant calls.\(^{38}\) A custom-developed, in-house software package (OncoSeek) was used to annotate sequence variants and to interface the data with the IGV. Nomenclature of genetic variants was designated following the Human Genome Variation Society recommendations.\(^{39}\) The limit of detection of the NGS assays was 1%.

### 2.3 | Statistical analysis

Overall survival was defined from the time of diagnosis to death from any cause. RFS and time to relapse were defined as the time from diagnosis or remission (CR/CRi) to first outcome event (induction failure, death during remission, or relapse), respectively. Patients who underwent stem cell transplant were censored. Statistical analysis was performed.
using GraphPad Prism 7 (GraphPad Software, Inc) and IBM® SPSS Statistics 24 (IBM, Inc). Fisher’s exact test and Mann-Whitney U test were used to assess categorical and continuous variables, respectively. Survival probability was determined using the Kaplan-Meier method, with difference compared by the log-rank test. A Cox proportional-hazards model was used for univariate and multivariate analysis. A \( P \)-value (two-sided) under .05 was considered statistically significant.

### 3 | RESULTS

#### 3.1 | Patient characteristics

The study cohort includes 27 patients, 23 men and 4 women, with the median age at diagnosis of 37 years (range: 18-75 years) (Table 1). The median hemoglobin level was 10.3 g/dL (range: 5.8-16.9 g/dL); leukocyte count \(14.5 \times 10^9/L\) (range: 1-137 \(\times 10^9/L\)), and platelet count \(123 \times 10^9/L\) (range: 13-327 \(\times 10^9/L\)). The median blast count was 80% (range: 6%-96%) and 61% (range: 0%-100%) in BM and PB, respectively. Immunophenotype included early T-cell precursor (\(n = 9\)), double negative (\(n = 8\)), double positive (\(n = 4\)), and single positive (\(n = 6\)).

Conventional cytogenetic analysis was available in 25 patients. These included 12 patients with normal karyotype, 4 with a simple abnormality (<3 abnormalities), and 9 with a complex karyotype (≥3 abnormalities). Well-known translocations involving T-cell receptor gene loci, t(10;11)(p13;q14), or t(11;19)(q23;p13) were not present. Monoclonal T-cell receptor gene rearrangements (\(TRG\) and/or \(TRB\)) were detected in 19 (76%) patients. All patients were treated with the standard chemotherapy regimen of hyper-CVAD (\(n = 6\)) or hyper-CVAD + nelarabine (\(n = 21\)).

#### 3.2 | High rate of complete remission (CR/CRi) after hyper-CVAD ± nelarabine regimen

Twenty-six (96%) patients achieved CR/CRi after the first or second course of induction chemotherapy. Eight of 26 (31%) patients relapsed at a median interval of 9.3 months (range: 3.2-18.2 months) after remission. With a median follow-up

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**Table 1** Clinical and laboratory characteristics of patient cohort

| Feature                     | Total (\(n = 27\)) | Low risk (\(n = 18\)) [w/o. RAS or TP53 mut] | High risk (\(n = 9\)) [w. RAS or TP53 mut] | \(P\)-value |
|-----------------------------|--------------------|---------------------------------------------|------------------------------------------|-------------|
| **Gender**                  |                    |                                             |                                          |             |
| Male                        | 23                 | 18                                          | 7                                        | .57         |
| Female                      | 4                  | 2                                           | 2                                        |             |
| **Median age (y) (range)**  | 37 (18-75)         | 42 (20-70)                                  | 26 (18-75)                               | .56         |
| **White blood cell count**  |                    |                                             |                                          |             |
| \(\times 10^9/L\) (range)    | 14.5 (1-137)       | 28.5 (2-108)                                | 9.3 (1-137)                              | .77         |
| **Platelet** \(\times 10^3/\mu L\) (range) | 123 (13-327) | 177.5 (13-327) | 53 (13-203) | .06 |
| **Hg (g/dL) (range)**       | 10.3 (5.8-16.9)    | 10.4 (5.8-16.9)                             | 10.2 (7.6-15.4)                         | .80         |
| **Blast % (range)**         |                    |                                             |                                          |             |
| **Bone marrow**             | 80 (6-96)          | 75.5 (6-94)                                 | 82 (45-96)                              | .19         |
| **Peripheral blood**        | 61 (0-100)         | 65.5 (0-100)                                | 32 (0-90)                               | .63         |
| **Cytogenetic (\(n = 25\))** |                   |                                             |                                          |             |
| Normal                      | 12                 | 8                                           | 4                                        | .99         |
| Simple                      | 4                  | 3                                           | 1                                        |             |
| Complex                     | 9                  | 6                                           | 3                                        |             |
| **TR gene subsets**         |                    |                                             |                                          |             |
| Gamma only                  | 5                  | 4                                           | 1                                        | .99         |
| Beta                        | 14                 | 8                                           | 6                                        |             |
| Germline                    | 6                  | 4                                           | 2                                        |             |
| **3-y overall survival**    | 50%                | 72%                                         | 36%                                      | .02         |
of 22.6 months (range: 3.8-49.7 months), 15 (65%) patients were alive and the 3-year OS rate was 50%. The median OS was 32.6 months.

### 3.3 Commonly mutated genes in T-ALL

Twenty-six (96%) patients had mutations in at least one of the tested gene. Fourteen (52%) patients showed a total of 19 NOTCH1 mutations. Recurrent hotspot mutations were not seen in NOTCH1. The median mutant allelic frequency (MAF) was 29% (range: 2.3%-53.5%) indicating a heterozygous change in most cases. Six patients had NOTCH1 mutation with a MAF < 10%. Three of these patients had other major mutant clones in NOTCH1 (patients #2 and 4) and TP53 (patient #7), respectively. NOTCH1 mutation was the only mutation in the remaining three patients (patients #8, 10, and 12) who had 81%, 32%, and 24% blasts in bone marrow, respectively.

Other recurrently mutated genes in this cohort were NRAS (n = 6), DNMT3A (n = 5), KRAS (n = 4) and TP53 (n = 2) (Table 2). The median MAF of the NRAS mutations was 37.8% (range: 3.6%-48.2%). Two patients had NRAS mutation with a MAF < 10%; both had major mutant clones in NOTCH1 (patients #2 and 4). Five of 6 patients with NRAS mutation also had a NOTCH1 mutation. The median MAF of DNMT3A mutation was 41.5% (range: 2.6%-49.8%). None of the 5 patients with DNMT3A mutation had a NOTCH1 mutation. KRAS mutations were mostly subclonal (median MAF: 5.5%) and 2 of 4 KRAS-mutated patients with MAF < 10% had mutations in other genes. In contrast, TP53 mutations were major clones (MAF: 93.5% and 25.4%). The two patients with TP53 mutation also had NOTCH1 mutation. Mutations in FBXW7 and PTEN were not detected in the study cohort.

### 3.4 N/F/R/P binary risk model did not stratify T-ALL patients treated with hyper-CVAD-based regimen

As a single mutation, no significant differences in outcome were observed in patients with NOTCH1, NRAS, or DNMT3A mutation (Figure 1A-F). However, patients with TP53 mutation had a poor outcome (Figure 1G,H). Meanwhile, the N/F/R/P binary risk model suggested by Trinquand et al29 failed to adequately stratify the patients in this cohort (Figure 2A,B). We further analyzed survival outcome of 4 groups in this cohort based on the mutational status of NOTCH1 and RAS, which did not demonstrate satisfactory risk stratification (Figure 2C). In the patient group with wild-type NOTCH1, the presence of RAS mutation predicted a poorer prognosis (P = .01). In the group with NOTCH1 mutation,
however, outcome was similar irrespective of RAS mutation \((P = .93)\). Given the fact that TP53 mutation was co-mutated with NOTCH1, we re-classified the group based on NOTCH1 and RAS/TP53 mutations. The new 4-group risk model showed improved stratification in outcome (Figure 2D). Since NOTCH1 mutation did not show much difference in RAS/TP53 wild-type group and mutated patient groups, we further simplified stratification of patients into 2 groups based on RAS/TP53 mutation irrespective of NOTCH1 status (low-risk \([n = 18]\): RAS and TP53 wild-type, high-risk \([n = 9]\): RAS or TP53 mutated, hereafter will be referred to MDACC risk groups). This new risk model showed significant risk stratification in both OS \((P = .03)\) and RFS \((P = .04)\) (Figure 2E,F).

### 3.5 End-of-induction measurable residual disease (MRD) by flow cytometry did not predict patient outcome

The status of MRD was assessed with MFC at the end of first and/or second induction in all but one patient who had refractory disease. Eighteen (69%) and 8 (31%) patients showed a positive and negative MRD at the end of induction chemotherapy. The status of MRD by MFC did not demonstrate significant difference in survival (Figure 3A,B). MDACC risk model further separated two prognostically different groups both in patients with positive MRD \((P = .02)\), but not in those with negative MRD \((P = .23)\) (Figure 3C,D).
3.6 Low white blood cell counts are associated with poor OS in T-ALL

Prognostic impact of white blood cell count (WBC) is less firmly established for adult T-ALL than for the pediatric T-ALL. High WBC of $\geq 100 \times 10^9/L$, however, is commonly considered a high-risk factor for both adult and pediatric T-ALL. In our cohort the median WBC was $14.5 \times 10^9/L$ (range: 1-137 $\times 10^9/L$) and only two patients (# 6 and 26) had WBC $> 100 \times 10^9/L$ at the time of diagnosis. Due to the skewed distribution to the lower

**FIGURE 2** Probability of OS and RFS in our patient cohort based on different combinations of gene mutations at the time of diagnosis. A and B, Low-risk and high-risk groups were determined according to the NFRP model (low risk: NOTCH1/ FBXW7 mutated and RAS/PTEN wildtype and; high risk: RAS or PTEN mutated). C, Different combinations of NOTCH1 and (N/K/RAS mutations. D, Different combinations of NOTCH1 and combined (RAS or TP53) gene mutations. E and F, Low-risk and high-risk groups were determined according to the MDACC model (low risk: RAS or TP53 wild-type; high risk: RAS and/or TP53 mutation). MDACC, MD Anderson Cancer Center; mut, mutated; NFRP, NOTCH, FBXW7, RAS, PTEN; OS, overall survival; R/T, RAS or TP53; RFS, relapse free survival; wt, wildtype

**FIGURE 3** A and B, OS and RFS for patients with T-ALL based on measurable MRD in all patients. C and D, OS in patients with a positive (C) or a negative (D) MRD at the end of induction chemotherapy stratified based on MDACC risk classifier. MDACC, MD Anderson Cancer Center; MRD, minimal residual disease; OS, overall survival; RFS, relapse free survival; T-ALL, T-cell acute lymphoblastic leukemia.
WBC (<100 × 10^9/L), we performed an ROC curve calculation to select a cutoff of WBC for which the difference in survival is more significant. The WBC of 10.8 × 10^9/L shows the best discrimination. Based on the new discriminator, patients with WBC of <10.8 × 10^9/L (n = 9) had worse outcome compared with those with higher WBC (≥10.8 × 10^9/L) (n = 18) (median OS: 14.6 months and not reached, respectively, \( P = .02 \); median RFS: 13 months and not reached, respectively, \( P = .12 \)) (Figure 4A,B). Similar to the above subgroup analysis with respect to MRD status, MDACC risk model further separated two prognostically different groups both in patients with WBC of <10.8 × 10^9/L (\( P = .02 \)), but not in those with WBC of ≥10.8 × 10^9/L (\( P = .77 \)) (Figure 4C,D).

3.7 MDACC risk stratification is an independent factor predicting worse OS in adult T-ALL patients treated with the hyper-CVAD

In univariate analysis, both MDACC high risk and lower WBC had increased risk of death. MRD status did not show any statistically significant difference. In multivariate analysis, MDACC risk model remained to have an increased risk of death (hazard ratio: 4.9, 95% confidence interval: 1.213-19.621, \( P = .026 \)) (Table 3).

4 DISCUSSION

In this study, we have examined a relatively small cohort of uniformly treated adult T-ALL patients for whom a systematic mutation analysis for the most relevant genes in T-ALL were performed at the time of diagnosis and before the initiation of induction therapy. While studying such a homogenous group of patients from a rare entity such as T-ALL is valuable, it should be clarified that the outcome of the study is considered preliminary due to low number of patients in the cohort.

The mutational profile of adult T-ALL in our cohort is similar to that reported in the literature.14,40 Almost all patients in our cohort had a mutation(s) in at least one gene. NOTCH1 was the most common gene mutation, in over half of cases, followed by KRAS/NRAS and DNMT3A mutations in 26%, and 19%, respectively. NOTCH1 mutations were
usually a major clone (MAF ≥ 10%), but subclonal fraction (MAF < 10%) was not uncommon. NRAS mutation (22%) was more common than KRAS mutation (15%), but co-mutations in both NRAS and KRAS were found in 50% and 75% of NRAS- and KRAS-mutated T-ALL cases. Unlike other studies, DNMT3A mutation was mutually exclusive to NOTCH1 mutation in this cohort.41 TP53 mutation was rare in this study (2/27, 7%) which is similar to the frequencies identified in previous studies with much larger cohort of adult T-ALL patients (between 5% and 11%).42,43 We did not observe any alterations in the FBXW7 and PTEN genes.

NOTCH1 mutation has been associated with a favorable outcome in most of earlier studies.11-14 However, in this study we did not observe a favorable outcome for patients with NOTCH1 mutation (Figure 1A,B). We also analyzed patients with a major NOTCH1 mutant clone (MAF > 10%), but a favorable outcome was not observed (data not shown). As the presence of mutations in TP5342,43 or RAS17 at the time of diagnosis of T-ALL have been reported to be correlated with an unfavorable outcome, and seven of 14 NOTCH1-mutated patients also had mutations of K/NRAS or TP53, we speculated that this unexpected negative result may be due to presence of the co-mutation. Nevertheless, exclusion of TP53- or K/NRAS-mutated cases did not reveal any favorable outcome for NOTCH1 mutated cases (data not shown). Similarly, RAS mutation was not associated with a poorer outcome in our cohort (Figure 1C,D), which showed prognosis in other studies.17,44 Furthermore, when we applied the N/F/R/P classifier, we did not observe any prognostic discrimination in our cohort (Figure 2A,B). However, when we divided our patients into 4 groups based on wild-type or mutated NOTCH1 and RAS, it did not show satisfactory stratification (P = .1) (Figure 2C). Focusing on the NOTCH1 wild-type subgroup, the presence of a RAS mutation showed a poorer prognosis (P = .01). However, in the NOTCH1-mutated subgroup, outcome was similar irrespective of RAS mutation (P = .93). We noticed that TP53-mutated patients in our cohort also had co-mutation in NOTCH1. We hypothesized that TP53 mutation could have negative effect on survival in NOTCH1-mutated patients, and re-classified our cohort based on NOTCH1 and RAS/TP53 mutation. This approach demonstrated improved risk stratification (P = .05) (Figure 2D). In this stratification model, NOTCH1 mutation did not further stratify patients in RAS/TP53-mutated (P = .89) and RAS/TP53 wild-type groups (P = .17). Therefore, we further simplified the risk model using only RAS and TP53 mutation (low risk: RAS and TP53 wild type, high risk: RAS or TP53 mutation), which showed improved risk stratification compared to the N/F/R/P model.

The N/F/R/P classifier failed to stratify T-ALL patients in our cohort. Presumably, the main reason is due to the fact that NOTCH1 mutation was not associated with favorable outcome in our cohort. Although reasons are unclear, the prognostic effect of NOTCH1 mutation in T-ALL might not be significant if patients are treated with non-BFM protocols. Indeed, lack of favorable outcome for NOTCH1 mutation in T-ALL has been reported, particularly in studies treated with regimen other than BFM-ALL protocols.45-48 Enrichment of ETP (33%) in our cohort could be attributable to the negative impact of NOTCH1 mutation since it is well-known for worse clinical outcome.49,50 However, to the best of our knowledge, it is unknown if N/F/R/P classifier retains prognostic power after stratified by immunophenotype. Cytogenetic aberrations do not seem to affect the result since our cohort demonstrates similar cytogenetic profile to previous studies.49,51 Instead, RAS and TP53 mutation could be the most significant factor for risk stratification.

Measurable residual disease status measured by flow cytometry after induction chemotherapy was not correlated with outcome in our cohort. However, application of our molecular risk model further identified patients with higher risk, showing the utility of our model. We found an inverse association between white blood cell count and outcome in adult T-ALL. Patients who had WBC of <10.8 × 10^9/L showed a significantly poorer OS compared to patient with higher WBC. Similar to MRD status, our molecular risk model further discriminated patients with WBC of <10.8 × 10^9/L. In univariate analysis, both MDACC molecular risk model and WBC count were significant risk factors but the former remains significant in multivariate analysis.

In summary, the N/F/R/P molecular classifier at diagnosis cannot be applied to adult T-ALL patients treated with hyper-CVAD with or without nelarabine. Instead, we found that RAS and TP53 mutations (MDACC risk model) showed improved stratification in adult T-ALL patients. The poor outcome of TP53 mutated T-ALL is in contrast to a recent report showed lack of the MDACC risk model was an independent risk factor in multivariate analysis. A larger, independent study is needed to confirm our data.

CONFLICT OF INTEREST
All authors have nothing to disclose.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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