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RISK STRATIFICATION TOOLS IN PREDICTING SURVIVAL AND TRANSFORMATION OF THERAPY-RELATED MYELODYSPLASTIC SYNDROME: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Therapy-related myelodysplastic syndromes (t-MDS) are grouped with therapy-related acute lymphoblastic leukemia (t-ALL) and therapy-related myelodysplastic/myeloproliferative neoplasms (t-MDS/MPN) under therapy-related myeloid neoplasms (t-MNs). Most myelodysplastic syndrome (MDS) prognostic models have excluded t-MDS patients, leaving their prognostic utility uncertain. **Objective:** This systematic review aims to synthesize the predictive utility of existing and novel risk stratification tools in assessing the survival and transformation of t-MDS. **Methods:** Searches were conducted in PubMed and ScienceDirect following PRISMA 2020 guidelines, focusing on overall survival and transforming t-MDS into acute myeloid leukemia (AML). Two reviewers independently screened references, extracted data, and assessed quality using the QUAPAS-2 tool. **Results:** From 1715 abstracts and 13 papers, 6 studies were included. Three studies on the International Prognostic Scoring System (IPSS) showed significant predictive power for survival and AML transformation. Five studies on the revised IPSS (IPSS-R) and WHO-based Prognostic Scoring System-revised (WPSS-R) also showed significant results. One study highlighted the cytogenetic component of IPSS-R (cIPSS-R) as highly prognostic. **Conclusion:** Existing and novel risk stratification tools demonstrate significant prognostic power for t-MDS. Further refinement and validation are needed to enhance risk assessment and treatment strategies.

Keywords: *Therapy-related Myelodysplastic Syndromes; Prognostic Stratification Tools; Survival and Transformation Prediction*

INTRODUCTION

Myelodysplastic syndromes (MDS) represent a diverse group of hematopoietic disorders characterized by ineffective hematopoiesis and a risk of progression to acute myeloid leukemia (AML)[1]. Therapy-related myelodysplastic syndromes (t-MDS) are a subset of MDS that arise as a consequence of chemotherapy or radiation therapy for a primary malignancy[2]. Therapy-related myelodysplastic syndrome patients often exhibit worse clinical outcomes compared to those with de novo MDS (d-MDS), which are MDS cases not associated with prior therapy[3,4].

Predictive models for MDS, such as the International Prognostic Scoring System (IPSS) and its revised version (IPSS-R), have been developed to stratify patients based on their risk and guide treatment decisions[5]. However, these models predominantly excluded t-MDS patients during their development, creating uncertainty about their prognostic utility in this subset of patients[6]. Given that t-MDS often presents with more aggressive clinical features and poorer prognoses, there is a tendency to treat these patients with more aggressive or palliative approaches[7].

To address this gap, it is essential to understand better the specific prognostic factors and risk stratification tools applicable to t-MDS[8]. This is particularly important as t-MDS, along with therapy-related acute lymphoblastic leukemia (t-ALL) and therapy-related myelodysplastic/myeloproliferative neoplasms (t-MDS/MPN), are classified under the broader category of therapy-related myeloid neoplasms (t-MNs)[9]. Accurate risk stratification of t-MDS can improve patient management by tailoring treatment strategies more effectively, potentially improving survival outcomes and quality of life for these patients[10].

This systematic review aims to synthesize the existing evidence on the prognostic utility of both established and novel risk stratification tools for t-MDS. By critically analyzing studies that have assessed these tools, we seek to clarify their effectiveness in predicting overall survival and transformation to AML in t-MDS patients. This comprehensive understanding is crucial for refining

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treatment protocols and ultimately improving patient care in this high-risk population.

METHODS

A systematic literature search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[11]. PubMed and ScienceDirect databases were searched using the following Boolean operators and key terms: ((((("t-MDS") OR ("therapy-related myelodysplastic syndrome")) OR ("Secondary MDS")) OR ("Secondary myelodysplastic syndrome")) AND ((((("PREDICTING FACTORS") OR ("IPSS-R")) OR ("PROGNOSTIC")) OR ("WPSS" OR "TPSS")).

Included in the review were research articles, clinical trials, and observational studies that examined prognostic factors or utilized risk stratification tools such as IPSS-R (International Prognostic Scoring System-Revised), WPSS (WHO-based Prognostic Scoring System), or TPSS (t-MDS Prognostic System). Studies reporting outcomes related to overall survival, progression-free survival, or transformation to acute myeloid leukemia (AML) were considered. Only studies published in English were included to ensure accessibility and clarity of data.

Excluded from consideration were studies not published in English, as well as reviews, editorials, commentaries, case reports, and conference abstracts. Studies that did not provide a distinct classification for therapy-related myelodysplastic syndromes (T-MDS) or specific prognostic outcomes, and those that solely presented diagnostic results, were also excluded. Additionally, studies lacking sufficient data or methodological rigor for assessing prognostic accuracy, those with inadequate sample sizes, or those with ambiguous outcome measures were excluded. Duplicate publications and studies without full-text availability were not considered.

Two independent reviewers performed the initial screening of titles and abstracts, followed by a full-text review of potentially eligible studies. Data extraction included capturing study characteristics, patient demographics, risk stratification methods, and outcomes of interest.

The methodological quality and risk of bias of included studies were assessed using the Quality Assessment of Prognostic Accuracy Studies (QUAPAS-2) tool, focusing on criteria such as participant selection, prognostic factor measurement, outcome assessment, and statistical analysis methods[12]. Any discrepancies between reviewers during the screening, data extraction, or quality assessment phases were resolved through consensus or consultation with a third reviewer.

RESULTS

Our systematic literature search initially screened a total of 1,715 abstracts. Based on our exclusion and inclusion criteria, 1,702 abstracts were excluded, leaving 13 full-text papers for further evaluation. Of these 13 papers, 3 were excluded due to lack of full-text accessibility.

We then proceeded to review the remaining 10 full-text papers. During this detailed review, 2 papers were excluded because they did not categorize therapy-related myelodysplastic syndromes (T-MDS) separately in the final prognostic analysis. Additionally, 2 more papers were excluded because they classified T-MDS together with other therapy-related myeloid neoplasms (T-MN) without distinguishing between them.

Ultimately, 6 studies met all inclusion criteria and were selected for detailed analysis and synthesis (Figure 1 and Table 1). These selected studies were evaluated for their relevance in exploring prognostic factors and risk stratification tools pertinent to T-MDS, including outcomes related to overall survival and transformation to acute myeloid leukemia (AML).

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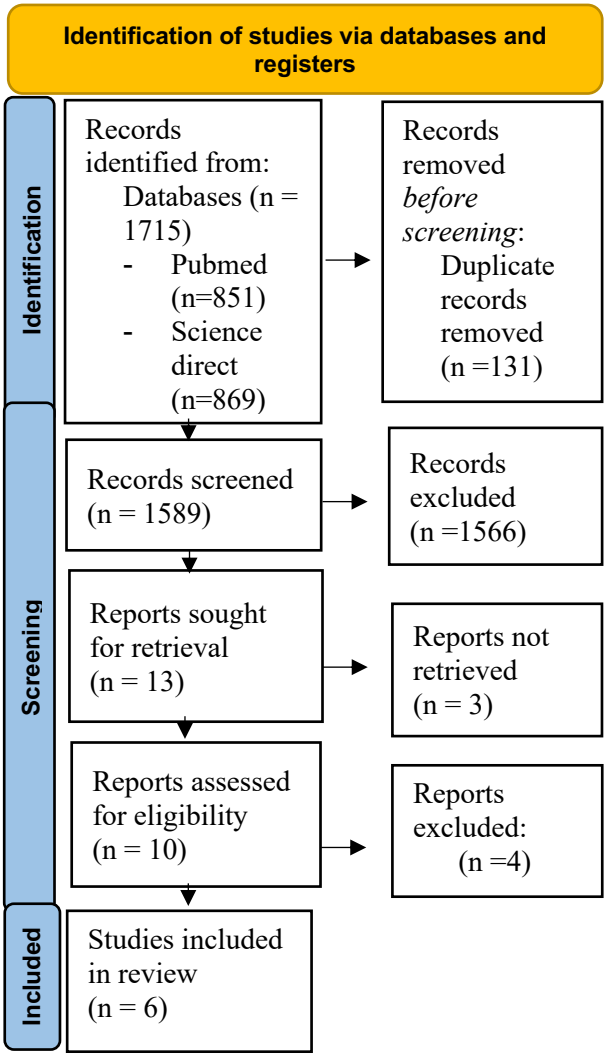

Figure 1. Prisma Flowchart

The quality assessment of the included studies was conducted meticulously using the Quality Assessment of Prognostic Accuracy Studies tool (QUAPAS-2).

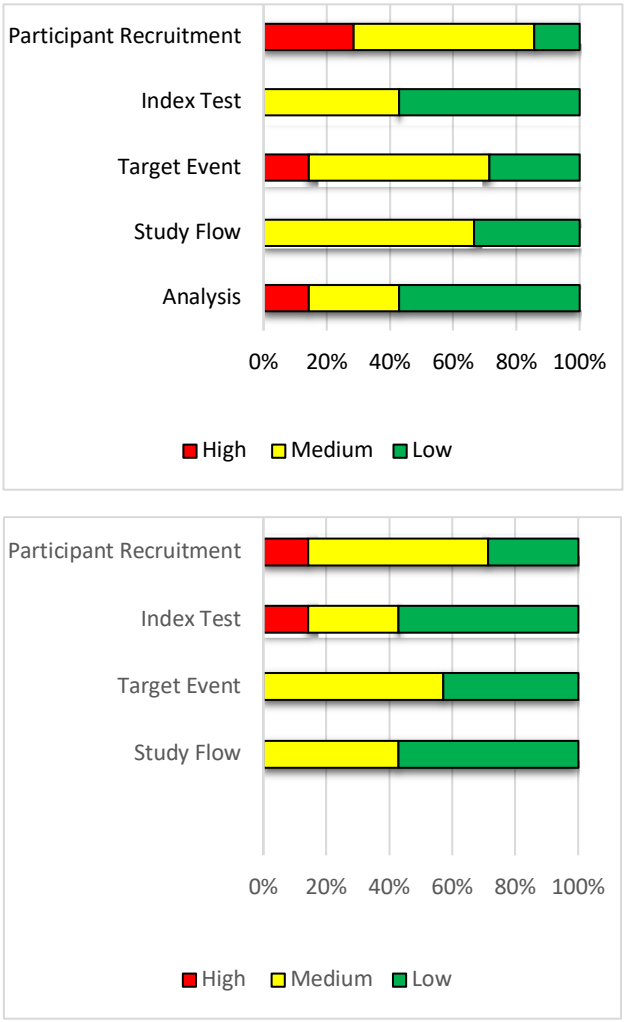

Figure 2. Quality Assessment of Prognostic Accuracy Studies tool (QUAPAS-2) consists of Risk of Bias (Up) and Applicability Concern (Down).

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Table 1. Studies included in the review

No	Authors, years of publication	Country	Size of sample	Methods	Outcomes
1	Quintas-Cardarma et al, 2014	USA	281	Cohort, retrospective	The International Prognostic Scoring System (IPSS) for therapy-related myelodysplastic syndromes (t-MDS) was highly effective in predicting overall survival ($p<0.001$). However, it did not distinguish significant survival differences between patients classified as intermediate-2 and high risk ($p=0.08$). In terms of Leukemia-Free Survival (LFS), all IPSS risk groups demonstrated significant differences ($p=0.001$), although no significant variations were found among the low, intermediate-1, and intermediate-2 risk groups ($p=0.2$).
2	Kuendegenet et al, 2021	US, Germany, Spain, Italy, Austria, and the Netherlands	2087	Cohort, prospective	IPSS-R showed better prediction accuracy compared to other models, with higher scores for AML-free survival (0.41 vs 0.37), overall survival (0.4 vs 0.38), and transformation risk (0.53 vs 0.36). This indicates it is effective in predicting outcomes for t-MDS patients. The cytogenetic part of IPSS-R also played a significant role in its predictive power. Similarly, WPSS demonstrated strong ability to predict prognosis in t-MDS, guiding clinical decisions for these patients.
3	Berggren et al, 2018	Sweden	1329	Cohort, retrospective	For therapy-related myelodysplastic syndromes (t-MDS), IPSS, WPSS, and IPSS-R showed C-index values of 0.71, 0.73, and 0.74, respectively. IPSS-R demonstrated superior predictive ability for overall survival (OS) in patients aged ≤70 years compared to IPSS ($P < 0.001$) and WPSS ($P = 0.01$), with a C-index of 0.76. Among patients >70 years, IPSS-R was superior to IPSS ($P = 0.002$), while differences with WPSS and IPSS were not significant. These scoring systems were particularly effective in predicting outcomes for younger t-MDS patients. Additional factors like age, gender, LDH levels, and transfusion requirements independently influenced OS. Patients with t-MDS generally had worse outcomes compared to de novo MDS, even after adjusting for these factors (HR 1.52, CI 1.21–1.90).
4	Zeidan et al, 2017	USA	370	Cohort, retropsective	Based on the analysis conducted, all prognostic models effectively distinguished overall survival (OS) among patients with therapy-related myelodysplastic syndromes (t-MDS) based on different risk categories. Each model showed significant differences in survival outcomes (log-rank $P < 0.001$). Patients with t-MDS consistently faced a higher risk of death compared to those with de novo MDS across all risk models, indicating poorer overall survival in t-MDS. The Akaike Information Criteria (AIC) scores further highlighted the predictive power of each model, with lower scores indicating better model fit: MDSS (2316), TPSS (2343), IPSS-R (2343), WPSS (2361), and IPSS (2364).
5	Cooper et al, 2019	USA	18	Cohort, retrospective	In patients with therapy-related myelodysplastic syndromes (t-MDS), a higher IPSS-R score (>3) was strongly linked with a higher risk of progressing to acute myeloid leukemia (HR, 1.8; 95% CI, 1.1-2.7; $P < 0.01$) and reduced overall survival (HR, 1.6; 95% CI, 1.2-2.2; $P < 0.001$).
6	Bernard et al, 2022	USA	234	Cohort, retrospective	Patients with therapy-related myelodysplastic syndromes (s/t-MDS), historically associated with high-risk disease, were enriched for complex karyotype (CK), TP53 multihit, PPM1D, and SETBP1 mutations. Specifically, 50% of s/t-MDS cases were categorized as IPSS-M high/very high, with an odds ratio of 2.3 (95% CI 1.8 to 3.1) compared to primary MDS.

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DISCUSSION

Our systematic review involved screening 1715 abstracts and 13 papers, ultimately selecting six studies that met our inclusion criteria. These studies evaluated various prognostic tools for therapy-related myelodysplastic syndromes (t-MDS), each offering distinct insights into their predictive accuracy and clinical applicability.

The International Prognostic Scoring System (IPSS) was assessed in three studies, all demonstrating significant prognostic power for overall survival (OS) and the transformation into acute myeloid leukemia (AML).[13,14,15] Additionally, one study highlighted IPSS's significant predictive value for Leukemia-Free Survival (LFS) ($p<0.0001$)[13]. However, another study found that IPSS failed to distinguish significant survival differences between patients with intermediate-2 and high-risk myelodysplastic syndromes (MDS) ($p=0.08$)[13].

Five studies focused on the revised IPSS (IPSS-R), all showing significant prognostic power[14-18]. Notably, one of these studies assessed the Dxy coefficient, revealing values (0.36-0.38) comparable to those observed in de novo MDS[16]. The WHO-based Prognostic Scoring System-revised (WPSS-R) was evaluated in three studies, all demonstrating significant prognostic value with a log-rank p-value <0.0001 and Dxy values ranging from 0.23 to 0.42, indicating robust prognostic discrimination not inferior to de novo MDS[14,15]. Another study assessed the cytogenetic component of IPSS-R (cipher), showing high prognostic power with Dxy values ranging from 0.25 to 0.33 across OS, LFS, and transformation outcomes[16].

The MD Anderson Global Prognostic System (MPSS) and t-MDS Prognostic System (TPSS) were evaluated in a single study each, demonstrating significant prognostic power ($p<0.0001$). Akaike Information Criteria (AIC) scores were used to assess the relative goodness of fit of these models, with lower scores indicating better predictive power: MPSS (2316), TPSS (2343), IPSS-R (2343), WPSS (2361), and IPSS (2364).

Furthermore, the novel clinical-molecular prognostic model, IPSS-Molecular (IPSS-M), captured heterogeneous risks in t-MDS and exhibited superior prognostic power for predicting LFS and OS compared to conventional tools ($p<0.0001$). However, its limited applicability in clinical settings was noted[15].

These findings underscore the diversity of prognostic tools available for evaluating therapy-related myelodysplastic syndromes (T-MDS), emphasizing the necessity for customized risk stratification approaches in clinical practice. This comprehensive assessment reveals significant variations in predictive accuracy and applicability among established systems such as IPSS, IPSS-R, WPSS-R, and novel models like IPSS-Molecular (IPSS-M). Each tool demonstrates distinct strengths in prognosticating outcomes such as overall survival (OS), leukemia-free survival (LFS), and transformation to acute myeloid leukemia (AML). This diversity advocates for the strategic integration of these tools into clinical decision-making to optimize patient management and outcomes[19,20].

Our study, while comprehensive, faced limitations, including the inability to access 3 journals that were initially considered during the first screening. Despite this, the robustness of our findings is supported by the rigorous analysis of the accessible studies, ensuring a solid foundation for our conclusions.

CONCLUSION

In conclusion, IPSS-R, traditionally used for MDS and not previously subjected to a systematic review for T-MDS, emerged as a reliable prognostic tool even for T-MDS. Other tools like IPSS and WPSS can also be employed but may require adjustments in several aspects for T-MDS. While IPSS-M showed promise as an effective prognostic tool, its complexity limits its routine use in clinical practice.

ETHICAL APPROVAL

There is no ethical approval for this systematic review.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

SR, BKKFTS, and ATR contribute equally in drafting, writing, and editing the manuscript.

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