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RISK STRATIFICATION FOR SURVIVAL AND TRANSFORMATION INTO ACUTE MYELOID LEUKEMIA IN PATIENTS WITH MYELODYSPLASTIC SYNDROME BASED ON THE PATHOGENICITY ASSESSMENT OF *TP53* MUTATIONS

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Summary

Introduction. Myelodysplastic syndromes (MDS) are diverse in terms of their appearance, symptoms, survival rate, and progression risk. A *TP53* mutation in a patient with MDS indicates a higher risk category, a lower chance of treatment success, a faster progression, and a poorer overall outcome. However, at present, there is insufficient focus on the degree of gene functional deficiency as a result of mutations.

The objective was to develop a system for risk stratification of patients with MDS by assessing the pathogenicity of *TP53* mutations.

Methods and materials. We performed a retrospective analysis of *TP53* mutations discovered during the 2022 International Working Group for the study of MDS research. The study was done on 2,343 adult patients with MDS without a known deletion in the *TP53* gene. Additionally, we reviewed the results of a separate study on the *TP53* gene, which involved patients with MDS as well as others with acute myeloid leukemia (AML). This study was conducted at Pavlov University.

Results. Based on the previously established classification algorithm, all patients were divided into three groups: those without a mutation in the *TP53* gene, those with a damaging mutation according to the classification system, and those with a neutral genetic variant according to it. There were differences in overall and leukemia-free five-year survival rates between groups of patients with MDS with damaging and neutral variants according to the developed system. Furthermore, a group of patients at the Pavlov University showed a difference in progression-free survival between groups of patients with MDS or AML with damaging and neutral variants according to our classification system.

Conclusion. The novel information system can be used to support medical decision-making in case of detection of variants of unknown significance in the *TP53* gene. The universality of the approaches used makes it possible to adapt the system to other genes and pathologies.

Keywords: molecular pathology, mutation, clinical significance, myelodysplastic syndrome, pathogenicity evaluation

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INTRODUCTION

Myelodysplastic syndrome (MDS) is a group of clonal diseases that affect the blood-forming stem cells. The treatment options for MDS vary widely, ranging from close monitoring to more aggressive therapies such as chemotherapy or stem cell transplantation.

To determine the most appropriate treatment plan for each patient, healthcare professionals use risk assessment tools such as the International Prognostic Scoring System (IPSS), the World Health Organization Prognostic Scoring System (WPSS), the Revised IPSS (IPSS-R), and others [1–3]. These tools help doctors evaluate the likelihood of complications and make informed decisions about the best course of action. IPSS was developed by researchers in 1997 and is used to assess the prognosis of MDS patients. The WPSS, created by the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) in 2008, helps predict the outcome of stem cell transplantation in MDS patients. Similarly, the IPSS-R, published in 2012, provides a revised version of the original IPSS system.

These risk assessment tools play a crucial role in guiding treatment decisions for MDS patients, helping healthcare professionals tailor care to each individual's unique needs and circumstances.

The most important indicators for determining the risk are the severity of cytopenia, the percentage of blasts in peripheral blood as well as bone marrow, and the presence and type of chromosomal abnormalities. It is widely known that, as the disease progresses, patients with MDS are more likely to develop mutations in the *TP53* gene. [4].

In general, somatic mutations in the *TP53* gene are most commonly found in malignant tumors and are associated with a poor prognosis. [5–7]. These mutations emerge in 5–10 % of MDS and acute myeloid leukemia (AML) patients, leading to decrease in overall survival rates and therapy effectiveness [4].

Previously, we created a highly specialized algorithm for classifying missense mutations according to their oncogenicity, population frequency, and evolutionary history [8]. It demonstrated higher sensitivity, specificity, and accuracy than any other predictor software for assessing the pathogenicity of genetic variants, which was shown on a set of known pathogenic mutations and benign variants from the ClinVar database. This type of analysis is standardly used to determine the operational characteristics of predictor programs to assess the pathogenicity of genetic variants [9, 10]. The classification system implies two groups of variants: damaging, with high predicted pathogenicity (analogous to oncogenic category in ClinGen/CGC/VICC classification), and neutral, with low predicted pathogenicity (analogous to somatic benign category in ClinGen/CGC/VICC classification), respectively.

We have decided to additionally evaluate our classification system with survival analysis. In this study, we analyzed overall, leukemia-free, and progression-free five-year survival rates of MDS and AML patients with damaging and neutral variants according to our algorithm.

The objective of the current study was to apply our recently developed variant classification system to categorize patients with *TP53* mutations into two groups with different likelihood of complications: those with damaging mutations and those with neutral variants.

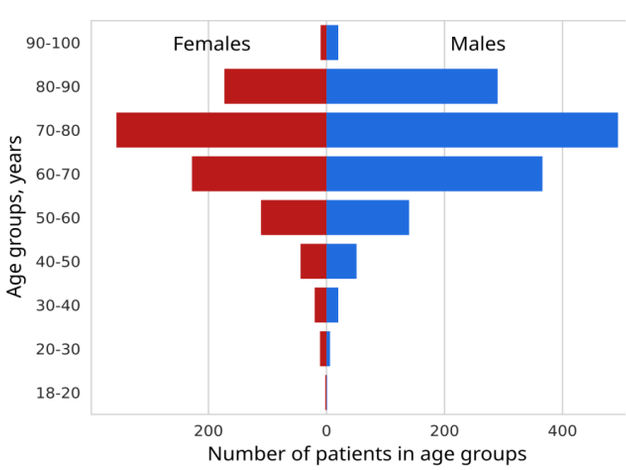


Fig. 1. Age and sex distribution of the participants

METHODS AND MATERIALS

The results of the *TP53* mutation analysis of 2,343 patients and their clinical data received from the International Working Group (IWG) for the study of MDS were obtained [11]. The inclusion criteria for the study were: age 18 years or older, a number of blasts in the blood less than 20 %, a white blood cell count less than 13×10^9/l, and a known mutation status of the *TP53* gene prior to starting therapy. Any abnormalities in the 17th chromosome, detected by cytogenetic methods such as karyotyping and fluorescent in situ hybridization, were used as an exclusion criterion. Follow-up was conducted for up to 5 years after diagnosis. The age and sex distribution of the participants in the study are shown in Fig. 1.

The cohort consisted of 1,388 men and 955 women, the age of patients ranged from 18 to 98 years, the median was 72 years (25th percentile – 63, 75th percentile – 78). Participants had one of the following diagnoses: unclassified myelodysplastic syndrome (MDS-U), MDS with isolated deletion of 5q (MDS-5q), MDS with excess blasts (MDS-EB), MDS with multilineage dysplasia (MDS-MLD), MDS with single lineage dysplasia (MDS-SLD), MDS-MLD with ring sideroblasts (MDS-RS-MLD), MDS-SLD with ring sideroblasts (MDS-RS-SLD), MDS-SLD/MLD, MDS-RS-SLD/MLD, and mixed myeloid pathology (MDS and myeloproliferative neoplasm (MPN), MDS-MPN with ring sideroblasts). The distribution of patients based on their diagnoses is shown in Fig. 2.

Additionally, the results of *TP53* mutation analysis in patients with MDS and AML from the Pavlov University between 2018 and 2023 were retrospectively analyzed. The inclusion criteria included individuals who were at least 18 years old and had an established diagnosis of MDS or AML. The follow-up period was up to 5 years after the diagnosis. This group consisted of 195 patients, including 98 women and 97 men. Their ages ranged from 18 to 79 years, with a median age of 51 and a 25th percentile of 41 and a 75th percentile of 60. Of these patients, 67 had AML, 52 were diagnosed with MDS-U, 46 had MDS-EB, 21 had MDS-MLD, three had MDS-5q, and two had mixed myeloid pathology. The remaining three patients had MDS-SLD, MDS-RS-MLD, and MDS-RS.

For the selection of patients with *TP53* mutations, we used recommendations on the interpretation of genetic variants associated with oncological diseases. [12]. Only patients with mutations corresponding to I, II, and III tiers were included (variants of strong, potential, and unknown clinical significance).

Pearson Chi-square test was used for qualitative features comparison between groups of patients:

$$\chi^2 = \sum_{i=1}^{r}\sum_{j=1}^{c}\frac{(O_{ij} - E_{ij})^2}{E_{ij}},$$

where r and c are the numbers of rows and columns in a contingency table, E_{ij} and O_{ij} are the expected and observed numbers of events in a cell of row i and column j.

In cases with the expected number of events in one of the cells of the contingency table was less than ten, a Fisher's exact test was used to compare groups of patients based on qualitative characteristics:

$$p = \frac{(a+b)!\,(a+c)!\,(c+d)!\,(b+d)!}{a!\,b!\,c!\,d!\,(a+b+c+d)!},$$

where a, b, c, and d are the numbers of two qualitative features observed in the two groups. Pairs of variables a and b describe a single variable of two groups, as well as c and d. Pairs of variables a and c are associated with a single group but different features, as b and d pair.

To compare the medians of the quantitative signs of different patient groups, the Kruskal–Wallis test was used:

$$H = (N-1)\frac{\sum_{i=1}^{g} n_i(\bar{r}_i - \bar{r})^2}{\sum_{i=1}^{g}\sum_{j=1}^{n_i}(r_{ij} - \bar{r})^2},$$

where N is the total number of observations across all groups, g is the number of groups, n_i is the number of observations in group i, r_{ij} is the rank of observation j in group i, $\bar{r}_i$ is the average rank for all observations of the group i, and $\bar{r}_i$ is the average rank for all observations.

In the case of comparing two groups of patients, we used the Mann – Whitney test:

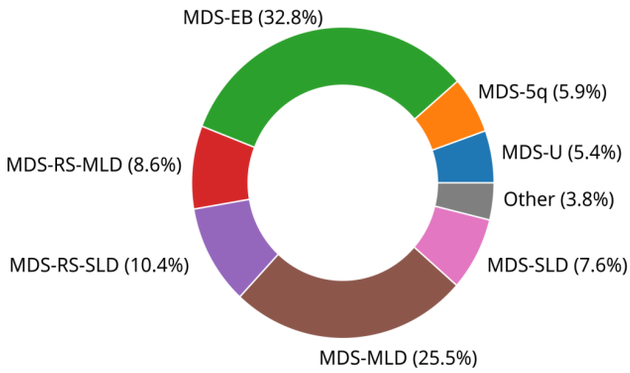


Fig. 2. Distribution of patients based on their diagnoses

$$U = n_x n_y + \frac{n_x(n_x+1)}{2} - T_x,$$

where n_x and n_y represent the sizes of the samples with larger and smaller rank sum, and T_x is the sum of ranks in the sample with the larger rank sum.

To solve the problem of multiple comparisons, the Benjamini – Hochberg method was used to calculate the adjusted p-value. The following formula describes the false discovery rate controlling procedure, used in the Benjamini – Hochberg method:

$$p \le \frac{i}{m}q^*,$$

where p is p-value, m is the number of comparisons, i is the rank of p in a sorted list in descending order, and q^* is the false discovery rate limit.

The Kaplan – Meier method was used to create survival curves:

$$S(t) = \prod_{t_i \in [0,t]}\left(1 - \frac{d_i}{n_i}\right).$$

The median survival was defined as the time period in which half of the patients in one group or the other experience an event.

The 95 % confidence interval for the survival function and median survival was calculated using the Greenwood's formula:

$$S(t) \pm 1{,}96\sqrt{S(t)^2\sum_{t_i \in [0,t]}\frac{d_i}{n_i(n_i - d_i)}},$$

where S is the survival function, i is the rank of timepoint, t_i is the time passed from the study start at the timepoint i, d_i is the number of events at the timepoint t_i, n is the number of observed subjects at the time t_i.

Restricted mean survival time (RMST) was additionally assessed, with condifence intervals calculated using the bootstrap merthod. The RMST was derived using the following formula:

$$\int_0^{\tau} S(t)dt,$$

where S is the survival function and is the time horizon.

When calculating the overall survival rate, only one event that was not censored was the death of a patient (endpoint). When calculating leukemia-free survival, a combined endpoint was used: uncensored events included death and transformation into acute myeloid leukemia. When calculating non-progressive survival, uncensored events included death and progression of MDS. The censored events included the discontinuation of follow-up in both groups, and the initiation of pathogenetic treatment (the use of chemotherapy or stem cell transplantation) in the IWG. A sensitivity analysis was conducted to assess the potential impact of informative censoring at the initiation of therapy. The survival analysis was repeated under a worst-case scenario assumption that the event (death/leukemic transformation) occurred immediately after the censoring timepoint. A competing-risk analysis using the Fine-Gray model was also performed to assess only leukemic transformation risk.

To evaluate the impact of the presence of a neutral and damaging *TP53* mutation on survival, a Cox proportional hazards regression model was employed, which can be generally described by the following formula:

$$h(t) = h_0(t) * exp(b_1X_1 + b_2X_2 + \ldots + b_pX_p),$$

where h is the hazard function, h_0 is the baseline hazard function, b_i are coefficients, and X_i are independent variables.

Cox's time-varying proportional hazard model was used to estimate the linear risk score with L2 penalty of 0.5.

Statistical calculations and graphical representation of the results were performed using Python libraries numpy, scipy, lifelines, matplotlib, seaborn, and R library cmprsk.

RESULTS

The classification of primary patients examined within the framework of the IWG was carried out. In this analysis, the fact of receiving pathogenetic treatment was censored which eliminated the effect of therapy on survival. According to the algorithm, 88 men and 83 women aged 19 to 92 years were classified as patients with damaging mutations in *TP53*, the median was 73 years, the 25th percentile was 65, the 75th percentile was 78.5 years. A group of patients with neutral variants was also identified. This group included 11 women and 13 men, aged 32 to 89, with a median age of 72, a 25th percentile of 62.5, and a 75th percentile of 77. The remaining patients did not have mutations in the *TP53* gene: among them were 1,287 men and 861 women, aged 18 to 98 years. The median age was 72 years, with a 25th percentile of 63 years and a 75th percentile of 78 years. We failed to find statistically significant differences in the distribution of patients by sex or age between these groups ($p>0.050$).

The overall five-year survival rate for two groups of patients with *TP53* variants and a group of patients without any mutations was analyzed. The median survival time and RMST were 23.1 (95 % confidence interval: 14.3, 46.6) and 30.9 (25.9, 35.9) months for the group of patients who had damaging *TP53* mutations based on the algorithm, and 59.1 (54.0, 60.0) and 43.1 (41.9, 44.3) months for the group without any mutations. For the group with neutral variants no median survival time could be determined, the RMST was 51.0 (41.7, 60.0).

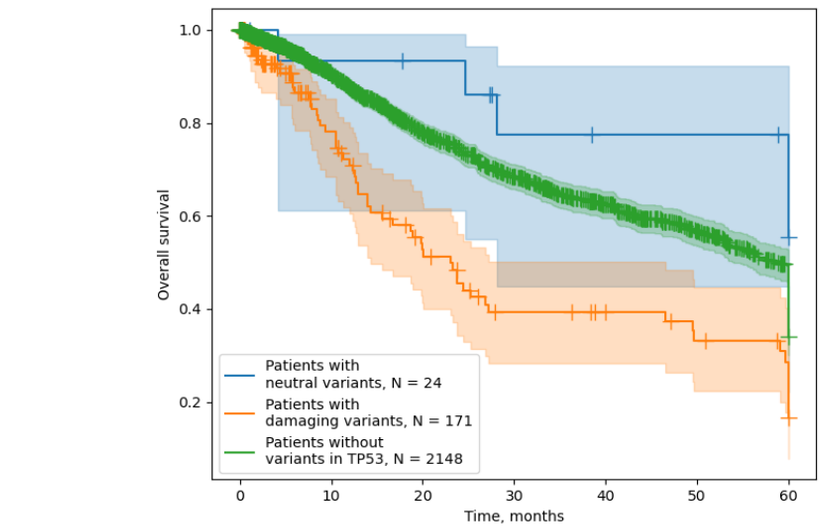
The five-year overall survival rate for the group of patients with damaging mutations was statistically significantly different from that of the group with neutral variants ($p=0.006$, $p_{adj}=0.008$), as well as the group without mutations ($p<0.001$, $p_{adj}<0.001$). Both conclusions were further supported by a sensitivity analysis using a worst-case scenario: $p=0.009$, $p_{adj}=0.014$ for groups with neutral and damaging variants; and $p<0.001$, $p_{adj}<0.001$ for groups with damaging variants and those with no variants in *TP53*. There were no significant differences in the five-year survival between patients with neutral variants and patients without *TP53* mutations ($p>0.050$, $p_{adj}>0.050$). The corresponding survival curves for each group are shown in Fig. 3.

The diagnoses of patients from different groups are presented in Table 1. Based on additional patient data, the IPSS-R and IPSS-M scores were calculated: IPSS-R takes into account values for hemoglobin, platelets, neutrophils, and bone marrow blasts, as well as the cytogenetic category while IPSS-M additionally considers the detected molecular markers.

The results of the additional classification of patients according to IPSS-M and IPSS-R scores are presented in Tables 2 and 3, accordingly.

We have found significant differences between all high and all low risk groups of patients with damaging *TP53* mutations and without mutations of *TP53* gene, in agreement with both IPSS-R and IPSS-M scales ($p<0.001$, $p_{adj}<0.001$). Both IPSS-R and IPSS-M also revealed differences in all high and all low risk groups between patients with damaging and neutral *TP53* variants according to the algorithm ($p=0.028$, $p_{adj}=0.042$ for IPSS-R and $p=0.026$, $p_{adj}=0.038$ for IPSS-M). There were no differences in all high and all low risk groups between patients without *TP53* mutations and neutral *TP53* variants ($p>0.050$, $p_{adj}>0.050$ using both scales).

The five-year leukemia-free survival of three groups of patients was also analyzed. Due to the fact that transformation into leukemia could not be confirmed for some of the patients, the composition of the groups changed: the group without mutations now consisted of 1,204 men and 815 women, aged 18–98 years (median age 72 years), and the group with damaging



Patients with neutral variants							
At risk	20	14	13	9	8	8	0
Censored	4	9	10	12	13	13	19
Events	0	1	1	3	3	3	5
Patients with damaging variants							
At risk	164	66	38	24	20	16	0
Censored	7	83	91	96	100	101	110
Events	0	22	42	51	51	54	61
Patients without TP53 variants							
At risk	2063	1187	841	647	479	335	0
Censored	85	817	1015	1113	1228	1333	1561
Events	0	144	292	388	441	480	587

Fig. 3. Curves of five-year overall survival for groups of IWG patients with and without *TP53* mutations. The survival curves and their 95 % confidence intervals are shown

Table 1

Diagnoses of IWG patients of different groups determined as a result of the algorithm

Diagnosis	Numbers and percents of patients with certain diagnosis in the group		
	Without *TP53* mutation	With neutral *TP53* variant according to the algorithm	With damaging *TP53* mutation according to the algorithm
MDS-U	77 (4 %)	–	3 (2 %)
MDS-5q	115 (5 %)	5 (21 %)	18 (11 %)
MDS-EB	678 (32 %)	8 (33 %)	82 (48 %)
MDS-MLD	565 (26 %)	6 (25 %)	26 (15 %)
MDS-SLD	172 (8 %)	2 (8 %)	4 (2 %)
MDS-RS-MLD	187 (9 %)	1 (4 %)	14 (8 %)
MDS-RS-SLD	232 (11 %)	1 (4 %)	10 (6 %)
Other	122 (6 %)	1 (4 %)	14 (8 %)

mutations consisted of 85 men and 77 women, aged 19–92 years (median age 72.5 years).

The survival curves are demonstrated in Fig. 4.

The median leukemia-free survival for patients with a neutral *TP53* variant according to the algorithm was not achieved, the RMST was 51.0 (40.7, 60.0) months. The median and RMST were 18.7 (13.0, 27.2) and 28.9 (23.5, 33.6) months among patients with damaging *TP53* mutations, 53.2 (50.5, 59.1) and 40.7 (39.3, 41.9) months among those without a mutation. Statistically significant differences were found in five-year leukemia-free survival between groups of patients with neutral and damaging mutations according to the algorithm ($p = 0.005$, $p_{adj} = 0.007$). We have also discovered differences in leukemia-free survival between patients with damaging and patients without *TP53* variants ($p < 0.001$, $p_{adj} < 0.001$). Both of these statements were confirmed by the additional survival analysis under a worst-case scenario assumption: $p = 0.008$, $p_{adj} = 0.012$ for groups with neutral and damaging variants; and $p < 0.001$, $p_{adj} < 0.001$ for groups with damaging variants and those with no variants in *TP53*. A competing-risk analysis using cumulative incidence function and Fine-Gray subdistribution hazards confirmed these findings ($p = 0.003$, $p_{adj} = 0.005$ for groups with neutral and damaging variants; $p < 0.001$, $p_{adj} < 0.001$ for groups

Table 2

IPSS-M scores of patients from different groups, defined by the algorithm

Risk group according to IPSS-M	Numbers and percents of patients with certain risk in the group		
	Without *TP53* mutation	With neutral *TP53* variant according to the algorithm	With damaging *TP53* mutation according to the algorithm
Very high	241 (12 %)	2 (10 %)	68 (43 %)
High	290 (14 %)	3 (15 %)	26 (16 %)
Moderate high	234 (12 %)	3 (15 %)	13 (8 %)
Moderate low	246 (12 %)	3 (15 %)	12 (8 %)
Low	722 (36 %)	5 (25 %)	33 (21 %)
Very low	287 (14 %)	4 (20 %)	8 (5 %)
All high	765 (38 %)	8 (40 %)	107 (67 %)
All low	1255 (62 %)	12 (60 %)	53 (33 %)

Table 3

IPSS-R scores of patients from different groups, defined by the algorithm

Risk group according to IPSS-R	Numbers and percents of patients with certain risk in the group		
	Without *TP53* mutation	With neutral *TP53* variant according to the algorithm	*With damaging TP53 mutation according to the algorithm*
Very high	99 (5 %)	3 (14 %)	54 (33 %)
High	261 (13 %)	3 (14 %)	30 (18 %)
Moderate	462 (22 %)	3 (14 %)	22 (13 %)
Low	881 (43 %)	9 (40 %)	43 (26 %)
Very low	364 (18 %)	4 (18 %)	15 (9 %)
All high	360 (17 %)	6 (27 %)	84 (51 %)
All low	1245 (60 %)	13 (59 %)	58 (35 %)
Low risk (total)	1255 (62 %)	12 (60 %)	53 (33 %)

with damaging variants and those with no variants in *TP53*).

Hazard ratio analysis showed no association between neutral variants and survival ($p>0.05$). However, damaging mutations were linked to shorter overall survival as well as leukemia-free survival in univariate ($p<0.005$) and multivariate design ($p<0.005$) including age, sex, karyotype, bone marrow blast count, hemoglobin, platelet count, neutral, and damaging *TP53* variants.

Moreover, multiparametric Cox model with time-dependent covariate for the receipt of pathogenetic treatment also demonstrates that the presence of a damaging *TP53* variant significantly impacts both the overall survival ($p=0.04$, Fig. 5, *a*) and the leukemia-free survival ($p=0.03$, Fig. 5, *b*).

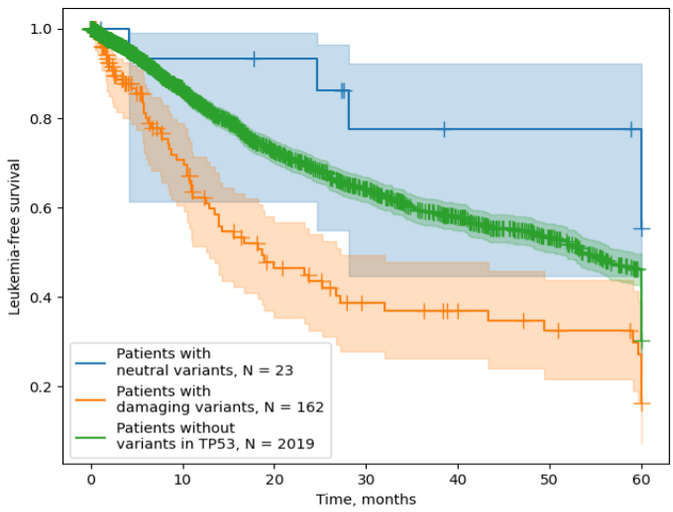
Additionally, a mixed group of patients with MDS and AML observed at Pavlov University was studied. There were both those who received chemotherapy before the start of follow-up and those who did not receive it. According to the algorithm, 17 men and 11 women aged between 29 and 70 were classified as having damaging *TP53* mutations. The median age for this group was 54 years, with a 25th percentile of 47.25 and a 75th percentile of 59. 19 women and 8 men aged between 25 and 79 years were classified as having neutral variants according to the algorithm. The median for this group was 55, with a 25th percentile at 50 and a 75th at 63. No *TP53* mutations were found in 78 women and 71 men, with an age range of 18–75 and a median of 50. The 25th and 75th percentiles were 40 and 60, respectively. There were no significant differences in the ages of patients from the different groups ($p_{adj}>0.050$).

The five-year overall and progressive-free survival rates were analyzed. No significant differences were found in the overall five-year survival.

We have found significant differences in progression-free survival between groups of patients with neutral and damaging variants according to the algorithm ($p=0.012$, $p_{adj}=0.036$).

The diagnoses distribution of the three patient groups as defined by the algorithm is presented in Table 4.

Analysis of the diagnoses distribution of patients with AML and MDS by groups without *TP53* variants, with neutral or damaging *TP53* mutations according to the algorithm, showed that there were no



Patients with neutral variants							
At risk	20	14	13	9	8	8	0
Censored	3	8	9	11	12	12	18
Events	0	1	1	3	3	3	5
Patients with damaging variants							
At risk	158	60	33	22	17	14	0
Censored	4	73	81	87	91	92	100
Events	0	29	48	53	54	56	62
Patients without TP53 variants							
At risk	1966	1082	742	567	417	305	0
Censored	53	737	922	1016	1115	1197	1395
Events	0	200	355	436	487	517	624

Fig. 4. Curves of five-year leukemia-free survival for groups of IWG patients with and without *TP53* mutations. The survival curves and their 95 % confidence intervals are shown

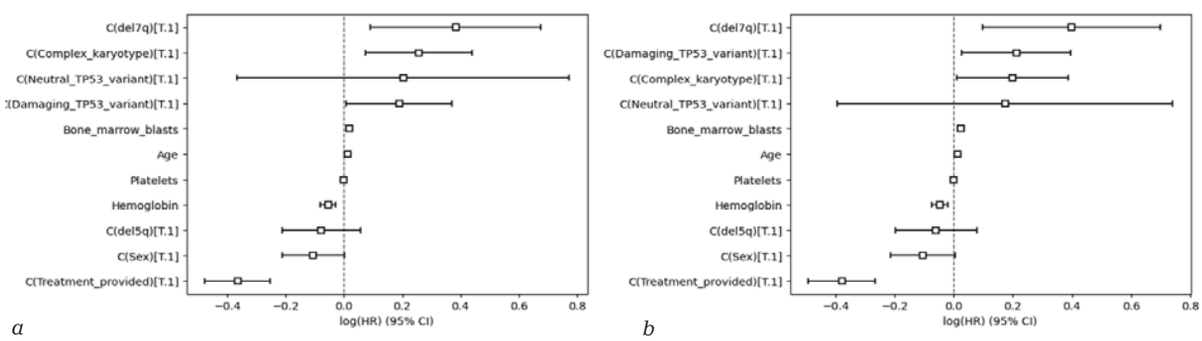


Fig. 5. Forest plot of multiparametric Cox model: HR — hazard ratio, CI — confidence interval

significant differences between groups ($p>0.050$, $p_{adj}>0.050$).

DISCUSSION

In this study, we assessed the clinical outcomes of functionally neutral and damaging *TP53* variants. We discovered that there is a subset of functionally neutral *TP53* variants that are not associated with shorter survival, in contrast to other mutations in this gene.

Generally, it is considered that all pathogenic mutations of the same gene equally impair the function of its protein product, making it unnecessary for patient evaluation to assess each individual mutation associated with the disease. However, there are known harmful variants that lead to different clinical outcomes, such as *CALR* type 1 and type 2 mutations [13]. There is also a wide range of outcomes for *TP53* mutations [14], which is not reflected in the currently used risk assessment scales such as IPSS-M [11].

We have evaluated MDS clinical features of patients with functionally damaging (pathogenic) as well as functionally neutral *TP53* mutations and found out that there was a statistically significant difference in overall and leukemia-free survival between primary MDS patients with damaging and neutral *TP53* variants. Additionally, we demonstrated that patients with neutral and damaging mutations differ in IPSS-M scale risk evaluation, with more high-risk patients having damaging *TP53* mutations. Hazard ratio analysis showed the link between survival and a presence of damaging *TP53* mutation, while such association was not found for neutral *TP53* variants.

Finally, we have discovered a statistically significant difference in progression-free survival between patients with neutral and damaging

Table 4

Diagnoses of Pavlov University patients of different groups determined as a result of the algorithm

Diagnoses	Numbers and percents of patients with certain diagnosis in the group		
	Without *TP53* mutation	With neutral *TP53* variant according to the algorithm	*With damaging TP53 mutation according to the algorithm*
AML	44 (31 %)	11 (41 %)	12 (43 %)
MDS-U	41 (43 %)	8 (50 %)	3 (19 %)
MDS-EB	36 (38 %)	2 (13 %)	8 (50 %)
MDS-MLD	12 (13 %)	5 (31 %)	4 (25 %)
MDS-5q	3 (3 %)	–	–
Other MDS	4 (4 %)	1 (6 %)	1 (6 %)
All MDS	96 (69 %)	16 (59 %)	16 (57 %)

mutations in a mixed AML/MDS set. However, no significant differences were found in the overall five-year survival in this set of patients. This fact may be explained by the presence of patients receiving treatment in this group which may have compensated for the functional insufficiency of the *TP53* gene in patients with damaging mutations, leading to a better outcome.

The main limitation of this study is the relatively small sample size of the compared groups, particularly the cohort of patients with neutral *TP53* variants. Although the initial dataset was large, the number of patients with molecular pathology was still insufficient. Consequently, our multivariate Cox regression model could not reliably accommodate the analysis of all potential predictors, including different chromosomal aberrations and point mutations in other genes, due to statistical power constraints.

We anticipate that the ongoing advancement of molecular diagnostics will facilitate the creation of larger, more comprehensively annotated datasets in the future. This will allow for refined variant classification into distinct subgroups, not just «pathogenic» and «benign», each with its own associated risk profile.

Conflict of interest

Authors declare no conflict of interest

Compliance with ethical principles

The authors confirm that they respect the rights of the people participated in the study, including obtaining informed consent when it is necessary, and the rules of treatment of animals when they are used in the study. Author Guidelines contains the detailed information.

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