Review

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Comparison of the WHO classification (5th edition) 2022 and the International Consensus Classification (ICC) 2022 for diagnosis of acute myeloid leukemia)

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Abstract: In 2022, two classifications were published to define the diagnosis of patients with acute myeloid leukemia (AML). The World Health Organisation (WHO) 5th edition and the International Consensus Classification (ICC) provide an updated summary of current knowledge of the diseases and construct a framework for physicians. Two differing classifications result in discrepancies, which change the definition of AML subtypes and present a challenge in clinical settings. This work summarizes the updated classification systems and discusses their significance in clinical settings while considering

the latest findings. Relevant changes affect the i) required blast percentage, ii) AML harbouring *CEBPA* mutations, iii) AML with *KMT2A* and *MECOM* rearrangements, iv) AML with myelodysplasia-related characteristics and in association with this entity AML with mutated *RUNX1*, and lastly v) AML with *TP53* mutation. In summary, a unified classification system would be desirable to achieve harmonized diagnosis and treatment of AML).

Keywords: AML, WHO, ICC

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Introduction

Acute myeloid leukaemia (AML), is one of the most aggressive hematologic malignancies with very poor prognosis. The median survival of patients with intermediate and high-risk settings is below one year [1].

The National Cancer Institute estimates that there will be around 20,380 new cases and 11,310 deaths this year in the United States [2]. To help navigate diagnosis and treatment in clinical settings, the World Health Organization (WHO) publishes classifications [3]. In 2022, the WHO issued the 5th edition of the classification of haematolymphoid tumours, based on basic research results and studies that have been conducted since the release of the "2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia" [4]. However, some of the authors, who had been involved in the preparation of the 4th edition of the WHO classification parted and published the first International Consensus Classification [5]. Analysis of these classifications reveal that most of their changes overlap and that their differences may cause confusion in clinical practice. This analysis compares the two classifications regarding their updates and their different approaches. It also discusses the implications of these differences and how they may pose difficulties in the diagnosis and management of AML patients.

Summary of both classifications

WHO 2022

The current state of research has led to incorporating more genetic features as criteria for AML subtypes, which resulted in the introduction of a new structure, dividing the subtypes in AML with defining genetic abnormalities and AML defined by differentiation [3]. The category AML with defining genetic abnormalities replaced the term AML with recurrent genetic abnormalities to express the importance of characteristic genetic findings as

diagnostic criteria [6]. Thus, the molecular aspect represented in a 20% blast cut-off is eliminated. This cannot be applied to AML defined by differentiation, where the blast cut-off is still required due to the absence of recognizable genetic abnormalities and to the distinction from MDS (Myelodysplastic syndrome, now renamed as MPN: Myelodysplastic neoplasms) [3].

For following subtypes within the category AML with defining genetic abnormalities, the 20% blast cut-off is however needed: AML with *BCR::ABL1* to distiguish from CML (chronic myeloid leukemia) and AML with *CEBPA* mutations due to insufficient knowledge about this subtype [3].

The latter was previously mentioned as biallelic mutation of *CEBPA biCEBPA* [6]. Now, the monoallelic *bZIP* mutation *smbZIP-CEBPA* (single mutations in the basic leucine zipper region) is also included [3]. Furthermore, AML with defining genetic abnormalities are listed as AML with rearrangements: AML with *t(9;11)(p21.3;q23.3);KMT2A-MLLT3* now changed to AML with *KMT2A* rearrangement and AML with *inv(3)(q21.3q26.2)* or *t(3;3)(q21.3;q26.2);GATA2::MECOM* to AML with *MECOM* rearrangement [6]. These adjustments in terminology correlate with the expansion of the gene fusion partners mentioned and with the intention to include all these partners by naming the entity after the key genes. [1, 6]. Other changes include the addition of AML with *NUP98* rearrangement and the subcategory AML with other defined genetic alterations, to insert subtypes with uncommon genetic findings, namely: AML with *RUNX1T3(CBFA2T3)::GLIS2*, with *KAT6A::CREBBP*, with *FUS::ERG*, with *MNX1::ETV6* and with *NPM1::MLF* [6]. Notably, the 5th WHO edition excludes the presence of a distinct entity of AML with mutated RUNX1 [6]. Likewise, the former entity AML-NOS (not otherwise specified) is now eliminated to allow for more detailed classification of AML [3].

The previous entity AML-MRC (myelodysplasia-related changes) has been replaced by the now genetically defined AML-MR (myelodysplasia-related) [1]. AML-MR poses another exception from the elimination of blast cut-offs. Before, only morphology and the 20% blast cut-off were considered as criteria. The 5th edition, however, includes updated cytogenetic criteria and eight defining somatic mutations, therefore assigning it to AML-MR with defining genetic abnormalities [3]. AML-MR is furthermore defined by the report of a previous diagnosis of MDN (formerly MDS) or MDN/MPN [3]. As a result, AML-MR is defined by two types: AML with a documented history of MDN or MDN/MPN and AML with a minimum of one genetic abnormality [6].

Alterations within the category of AML defined by differentiation include the change of terminology from pure erythroid leukemia to acute erythroid leukemia, to aim for more similarity with the other subtypes [6].

ICC 2022

The international consensus classification reveals substantial differences for diagnosis of AML compared to the WHO 2022 classification (Table 1). One significant modification has been implemented regarding the 20% blast cut-off in AML subtypes with recurrent genetic abnormalities, which now has been lowered to 10% [7]. AML with rearrangements of *MECOM* and *KMT2A* are divided by fusion partners: AML with *MLLT3::KMT2A* (or *GATA2::MECOM*) and AML with other *KMT2A* or *MECOM* rearrangements [1, 5].
Furthermore, the new category AML with other rare recurring translocations has been added. [5] AML with biallelic *CEBPA* mutations is replaced by the subtype AML with in-frame *bZIP CEBPA* mutations, focusing more on the location rather than the allelic status [1]. This definition poses as a restriction and excludes other types of *CEBPA* mutations [7].

However, the 20% cut-off is still valid for the subtypes AML with *BCR:ABL1*, to ensure distinction from CML, and the new entity AML with mutated *TP53* [7]. The 20% blast cut-off is required as criteria for AML with mutated *TP53* to distinguish it from MDS/AML (10-19%) or MDS (0-9%) [5]. MDS/AML is a new term introduced by the ICC consortium and replaces the former term MDS-EB2 [5]. Since MDS cases are defined with a blast cut-off lower than 10%, the new entity MDS/AML is introduced for cases that would fit in the diagnostic continuum between the categories MDS and AML, including the subtypes MDS/AML with mutated *TP53*, with MR gene mutations, MR cytogenetic abnormalities and MDS/AML, NOS. This new entity should make these patients suitable for MDS and AML trials [5].

The former subtype pure erythroid leukemia, now referred to as acute erythroid leukemia, is classified as AML with mutated *TP53* (in case of *TP53* mutation) [7]. This decision is based on the high prevalence of harboring a minimum of two *TP53* abnormalities [7]. The previous classification of AML with myelodysplasia-related changes is separated into AML with myelodysplasia-related (MR) gene mutations and AML with myelodysplasia-related cytogenetic abnormalities [1]. Noticeably, *RUNX1* mutations, are no longer an own entity but termed as AML with MR gene mutations – in contrast to the WHO 2022 classification [5].

Another significant change in nomenclature involves the elimination of certain definitions and the introduction of these as diagnostic qualifiers. These include AML cases that are therapy-related, cases that progress from MDS or MDS/MPN, and patients with a germline predisposition. Reducing these points to qualifiers, rather than a set definition, should avoid overlaps within other categories [7].

Table 1. Summary of discussed differences between WHO and ICC 2022.

	WHO classification 2022	**ICC 2022**
AML with recurrent genetic abnormalities	**AML with defining genetic abnormalities**	**AML with recurrent genetic abnormalities**
	AML with RUNX1::RUNX1T1 fusion AML with CBFB::MYH11 fusion Acute promyelocytic leukaemia with PML::RARA fusion AML with KMT2A rearrangement AML with DEK::NUP214 fusion AML with MECOM rearrangement AML with RBM15::MRTFA fusion AML with BCR::ABL1 fusion* AML with NUP98 rearrangement AML with other (rare) defined genetic alterations* AML with NPM1 mutation AML with CEBPA mutation	AML with t(8;21)(q22;q22.1)/ RUNX1::RUNX1T1 AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11 Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/ PML::RARA; APL with other RARA rearrangements AML with t(9;11)(p21.3;q23.3)/ MLLT3::KMT2A; AML with other KMT2A rearrangements AML with t(6;9)(p22.3;q34.1)/DEK::NUP214 AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2::MECOM (EVI1); AML with other MECOM rearrangements AML with BCR::ABL1 fusion* AML with other rare recurring translocations AML with mutated NPM1 AML with in-frame bZIP CEBPA mutations AML with mutated TP53 (VAF >10%)*
AML not otherwise specified	**AML, defined by differentiation** AML with minimal differentiation AML without maturation AML with maturation Acute myelomonocytic leukemia Acute monoblastic/monocytic leukemia Pure erythroid leukemia Acute megakaryoblastic leukemia Acute basophilic leukemia	**AML not otherwise specified** AML with minimal differentiation AML without maturation AML with maturation Acute myelomonocytic leukemia Acute monoblastic/monocytic leukemia Pure erythroid leukemia*** Acute megakaryoblastic leukemia Acute basophilic leukemia
Required blast count	no blast cut-off (excl. CEBPA and BCR::ABL1 AML and rare defined genetic alterations), → ≥ 20% for subtypes without defining genetic abnormalities	≥ 10% for all genetically defined subtypes → ≥ 20% for subtypes without defining genetic abnormalities and TP53 mutated AML
CEBPA mutation	biCEBPA mutation smbZIP-CEBPA	in-frame bZIP CEBPA (bi- and monoallelic)
Rearrangements	AML with KMT2A rearrangement	AML with t(9;11)(p21.3;q23.3)/ MLLT3::KMT2A; AML with other KMT2A rearrangements
	AML with MECOM rearrangement	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2::MECOM(EVI1) ; AML with other MECOM rearrangements

AML with myelodysplasia-related changes	**AML-MR** Defining cytogenetic abnormalities WHO Complex karyotype (≥3 abnormalities) 5q deletion or loss of 5q due to unbalanced translocation Monosomy 7, 7q deletion, or loss of 7q due to unbalanced tranlocation 11q deletion 12p deletion or loss of 12p due to unbalanced translocation Monosomy 13 or 13q deletion 17p deletion or loss of 17p due to unbalanced translocation Isochromosome 17q idic(X)(q13) Defining somatic mutations WHO ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2 Prior history of MDS or MDS/MPN remaining a diagostic premise in WHO but become qualifier in ICC	**AML with MR cytogenetic abnormalities** Defining cytogenetic abnormalities ICC Complex karyotype (≥3 abnormalities) del(5q)/t(5q)/ add(5q) Monosomy 7, 7q deletion Trisomy 8 del(12p)/t(12p)/add(12p) Monosomy 17/add(17p) or del(17p) Isochromosome 17q idic(X)(q13) del(20q) **AML with MR gene mutations** Defining somatic mutations ICC ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2, RUNX1
Eliminated subtypes	AML with RUNX1 mutation AML, NOS Therapy-related myeloid neoplasms (now new entity as secondary myeloid neoplasm)	AML with RUNX1 mutation Therapy-related myeloid neoplasms (now diagnostic qualifier)
Added subtypes/ criteria		AML/MDS (Blast count 10-19%) AML with mutated TP53 diagnostic qualifiers

*requiring > or = 20% blasts; ** blast count of 10 to 19% defined as MDS/AML in adult
***most cases are associated with TP53 mutations and should be classifed as AML with mutated TP53

Discussion

Blast cut-off

One key difference between the 5th WHO classification and the ICC is the blast cut-off. The blast cut-off should be in use to differentiate MDS from AML cases [3]. Before the 20% blast cut-off was implemented (WHO 4th edition), a 30% cut-off was used to determine whether a patient is eligible for MDS or AML therapy [8]. Definition of AML specific molecular and cytogenetic features led to the reduction of the required blast percentage in certain subtypes [3]. Bacher et al. suggested that cases of AML or MDS which falls between these categories, should be characterized by karyotype analysis and molecular abnormalities to ensure an accurate therapeutic decision [9]. Taking this into consideration, the newest WHO classification eliminated the blast cut-off for AML with defining genetic abnormalities [3].

In contrast, the ICC reduced the percentage to 10% for all genetically defined AML subtypes [5].

Both classifications, however, decided that when no AML-defining genetic alteration can be found, the 20% threshold must be used [3, 5]. Concerns, that patients with low blasts in their bone marrow or peripheral blood can be harmed when treated with AML-like therapy, have been expressed towards both classifications [10]. These decisions were made to find an approach for widening the possibilities of treatment for both diseases, MDS and AML. Due to the previous cut-offs, cases of MDS with >20% blasts and AML cases with <20% blasts were not included in clinical trials, thus there is not sufficient data on effectiveness when treated differently [8]. The ICC's newly introduced subcategory MDS/AML should represent the existing biological continuum, limited by the blast range of 10 to 19% [8]. A study comparing MDS types noted that 83% of cases with AML-like mutations showed blast percentages varying from 15 to 19% [11]. Furthermore, cases with 10-19% blasts were already treated successfully with AML-type treatments [10]. This subcategory is also based on the fact that there are biological similarities between certain MDS and AML types [8]. *Estey* et al. not only proposed the introduction of a new category of MDS/AML, but also defined the group's minimum blast percentage by 5%, which draws attention to the fact that blast percentage should play a less significant role [8]. *DiNardo* et al. emphasises that in clinical settings, more attention should be paid to the patient's age and fitness, alongside with cytogenetics and mutations. Younger patients (< 60 years old) should be treated with AML-type IC (intensive chemotherapy) as they showed similar OS regardless of the blast percentage [12]. Responses were better in the presence of a normal karyotype and/ or a *NPM1* mutations [12]. Similarly, younger patients with MDS-IB and at least 10% blasts showed an increased remission rate with better OS, supporting the established blast percentage for MDS/AML [12].

DiNardo et al. proposes for older, fragile patients with complex karyotypes and AML with mutated *TP53* or *MECOM-r* and patients with MDS to be treated with HMA-based treatments (hypomethylating agent). Furthermore, it was emphasised to prioritise biological features to distinguish between similar cases of MDS-IB and AML subtypes. Prospective studies for subjects with MDS- and AML are required. [8, 12].

CEBPA mutation

The classifications also differ by their AML categories containing mutations in the *CCAAT/* enhancer-binding protein alpha, short *CEBPA*, gene [13]. Before, the WHO introduced the entity AML with biallelic *CEBPA* mutation, as it was considered to have

favourable outcome. Little attention was paid to the monoallelic mutation because of studies showing similarities with the wildtype mutations [14]. It was pointed out that these studies grouped together cases of single mutations in the transactivation domain (TAD) located at the N-terminus with cases with mutations in the *bZIP* domain located at the C-terminus of the protein [15]. Further analyses of the single mutation cases recognized that not the allelic status but the location of the mutation led to a favourable prognostic phenotype [14].

Taube et al also discussed the association of favourable prognosis with in-frame *bZIP* mutations, by analysing similarities between mono- and biallelic mutations of that region [14].

Interestingly, *bZIP* and biallelic *CEBPA* mutations showed similar clinical and biological features. These patients were younger, showed higher white blood cell count and showed in comparison to other patients with different *CEBPA* mutations a higher OS and event-free survival (EFS). Interestingly, co-occurrence of *GATA2* mutations within the *bZIP* mutated cases were associated with better long-term survival [14]. Furthermore, the patient's age (when <65 years) correlated with prognosis as *biCEBPA* cases showed higher CR and better 5-year OS [13]. Taking these findings into account, the definition of a *CEBPA* subgroup in AML should focus more on the in-frame insertions or deletions in the *bZIP* domain, as it poses as a better prognostic marker than the biallelic mutation [13]. *Zhao* et al. showed that 69% of cases with mutations in the *bZIP* region were in-frame deletions or insertions [16]. The *CEBPA* gene is rich in guanine and cytosine and is thus difficult to target by PCR in contrast to the *bZIP* domain [13]. *Faisal* and *Sung* suggest re-classification of the biallelic cases harbouring two *TAD* mutations or cases with *bZIP* mutations not being in-frame and stresses that they should not be utilised for prognostic decisions [15].

Rearrangements

AML involving rearrangements of the key genes *KMT2A* and *MECOM* were also affected by changes in both classifications. WHO and ICC decided on including new fusion partners to the respective subgroups [3, 5]. However, the ICC added a new subgroup containing the novel partner genes, now dividing these cases in two different categories, the previous category (AML with *MLLT3::KMT2A* or with *GATA2::MECOM*) and the one with "other *KMT2A* or *MECOM* rearrangements" [5]. Whether these fusion partners should pose as a stand-alone category or can be put in one entity, as the 5th edition of the WHO suggests, cannot be evaluated correctly, for there is little to no data on prognostic features.

However, studies comparing rearrangements evolving *KMT2A* have not found significant differences in OS when comparing cases harbouring the *t(9;11)* translocation with

different translocations. [17, 18]. *Sánchez* et al. also draw attention to the fact that if differences can be noted, they may originate from co-occurrences of other mutations, thus stressing that prognosis is linked to the mutational landscape [17]. On the other hand prognostic differences have been described when comparing *t(9;11)(p22;q23)* cases with cases harbouring translocations with other *KMT2A* partners [19]. Comparison of *MECOM* rearrangement led to similar results. *Gao* et al. found that classic (i.e. common) and non-classic *MECOM-r* resulted in a poor prognosis, regardless of the translocation partner. Differences were only found in cytogenetic features and clinicopathology [20]. In conclusion, molecular features should be used to differentiate *MECOM-r* cases [21].

AML-MR; RUNX1

Definition of the previous AML subtype with myelodysplasia-related changes (AML-MRC) has been changed in both classifications. Cases meeting any of the following criteria were classified as AML-MRC before: the presence of (multi)lineage dysplasia, a documented history of MDS or MDS/MPN, or MDS-related cytogenetics [22]. Nevertheless, this definition lacked specific genetic aspects [22]. Studies showed that within the group of AML-MRC, most cases were presented with poor prognosis [23]. To help navigate cases under this subclassification, further studies investigated the genetic features.

Secondary AML (sAML) cases have been studied regarding mutational patterns, resulting in a pattern of eight genes, when mutated, to be specific to this subtype (*SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2*). [24] Furthermore, cases harbouring mutations in one of these genes are associated with poor survival [25]. The 5th edition of the WHO classification included these eight somatic mutations as MR gene mutations [22]. *Park* et al. found these alterations to be appropriate, as they describe a more homogenous group based on biologic characteristics. This would also affect treatment usage, as *Lindsley* et al. revealed that cases with MR gene mutations are less receptive to chemotherapy and would be stratified as adverse-risk [26]. The new definition of AML-MR ensured more cases to be classified as such, thus more cases could be precisely identified to a homogeneous group and therefore be treated accordingly. Thereby a significant number of former AML, NOS patients are now classified as AML-MR. This also supports the WHO's decision to eliminate the AML, NOS entity and introduce the AML defined by differentiation entity [25].

In addition, the ICC included the *RUNX1* mutation as the ninth of the MR gene mutations, as the ELN 2022 risk stratification stratifies the *RUNX1* mutation as adverse-risk. [27].

The 4th edition of the WHO's classification introduced the new category AML with mutated *RUNX1* as a stand-alone entity, given the data collected from studies showing distinct prognostic and biologic features being associated with cases harbouring the *RUNX1* mutation [28, 29]. However, it was criticized that these studies might have selected their cases, which led to the conclusion that mutated *RUNX1* drives poor outcomes [29]. Given the unclarity of the *RUNX1* mutations' role in prognosis, the WHO decided to eliminate the entity [26, 30]. A twofold increase in the frequency of *RUNX1* mutations were observed when cases harboured a mutated MR gene, supporting the elimination of the category AML with RUNX1 mutation. *Rungjiraittaron* et al. documented similarities in survival when comparing cases of de novo AML with mutated *RUNX1* and intermediate-risk cytogenetics and AML with wildtype *RUNX1*. Thus, the study concludes that *RUNX1* mutations are not a reliable independent prognostic factor and cannot be categorised with the adverse-risk MR gene mutations [26]. *McCarter* et al. analysed the predictive value of cases with and without *RUNX1* mutations within the AML-MR gene mutation category, concluding that the exclusion of *RUNX1* would result in a 4% increased AML-MR identification rate [31]. Furthermore, the significance of including the antecedent history of MDS or MDS/MPN as a criterion was discussed, as this is another difference among these classifications. The ICC newly introduces diagnostic qualifiers, one of them being the recorded history of MDS or MDS/MPN, or cases of therapy-related AML. This would alter hierarchy in diagnosis, as the genetic definition gains priority over the ontogeny. However, *McCarter* et al. suggest that the MR gene mutations, including *RUNX1*, are not solely responsible for adverse-risk features and ontogeny must be recognised as an independent prognostic factor. Moreover, their study estimates cases of AML with MR gene mutations to be stratified between favourable- and intermediate-risk. As the cases of secondary AML showed inferior outcome, they propose that AML-MR must be defined by ontogenesis and MDS-associated cytogenetics. Further findings support this definition, as the cases with documented history of MDS showed inferior survival [22, 27].

TP53 mutation

Mutated *TP53* displays a challenge for physicians due to very poor prognosis and low response to common regimens (induction chemotherapy, hypomethylating agent-based treatments and venetoclax-based therapy) [32]. In 2017 the ELN stratified this AML subtype – commonly associated with a complex karyotype (CK) – as adverse risk population [7, 33]. The recent update of the stratification in 2022 implements a new hierarchy and adds changes to the therapy-related AML and AML-MR subgroups. Now, the presence of a *TP53*

mutation is put first in hierarchy, in case the variant allele frequency is higher than 10%. The newly added criterion should apply to subgroups of MDS/AML and AML, while it is not listed as criterion if the *TP53* mutation status applies to one or both alleles [33]. Taking this into consideration, the ICC introduces the new category of myeloid neoplasms with mutated *TP53*, including MDS (0-9% blasts), MDS/AML (10-19%) and AML (>19%). [5] In contrast, the WHO 2022 did not introduce a separate category of AML with mutated *TP53* [3]. The decision on the novel subgroup in the ICC classification is based on studies showing that *TP53* mutated cases shared similar clinical characteristics, regardless of MDS or AML diagnosis and ontogeny (de novo, therapy-related) [7]. *McCarter* et al. conclude that ontogeny in context of *TP53* mutations plays a less significant role and therefore support the inclusion of the distinct subgroup [31]. However, the discussion on dividing the myeloid neoplasm cases according to set blast counts is debated on. Studies comparing AML and MDS-EB cases with mutated *TP53* revealed similar prognosis [33]. Thus, clinical characteristics are not associated with MDS or AML diagnosis and BM blast percentage, while the presence of a complex karyotype (CK) is believed to be the important criterion [32]. Although including blast counts and thus dividing these cases, the ICC did change the hierarchy in diagnosis significantly arguing that further research might result in better treatment [31]. However, a unified category might reduce subdivision of trials and facilitate approval of therapies, since many of them are limited to AML or MDS and to ontogeny (de novo or secondary) [34]. Apart from blast count, the ICC implements other criteria to be met within the *TP53* entity. *TP53* mutated MDS cases should show either a multi-hit mutation or a complex karyotype [5]. In contrast, the MDS/AML and AML entity can exhibit any pathogenic *TP53* mutation, given a VAF > 10% [5, 7] Studies comparing de novo AML with mono-allelic *TP53* mutation according to VAF noted that within the range of 20 to 40% VAF there are no differences in OS in cases treated with HMA (with or without VEN). In association with cytarabine-based treatment, OS and response rates were worse the higher the VAF [35-37]. It remains unclear, whether a 10% threshold is suitable as a criterion for AML, as there are few studies available on this topic. *Hiwase* et al. consider the 10% threshold as appropriate, as it could help identify patients with poor outcomes [38].

Similarly, *Shah* et al. compared therapy-related cases of AML and MDS and found that a VAF exceeding 10% led to a poorer prognosis [38, 39]. *Weinberg* et al. claim a certain homogeneity of MDS and AML cases with mutated *TP53* in presence of a CK, as it is associated with worse OS [33, 34]. Since most of *TP53* mutated cases are associated with CK, the authors of the ICC presumably decided to exclude this factor from the definition [33]. Another reason for discussion is whether the allelic status indicates certain outcomes.

Weinberg et al. states that the amount of functioning protein and therefore the presence of a mono- or biallelic mutation affects clinical characteristics [7]. *Grob* et al. found similarities in survival when comparing monoallelic and biallelic mutated AML and MDS-EB cases [40]. In contrast, other findings report similarities in monoallelic and wild-type cases [7]. A recent study revealed differences in OS showing that cases of biallelic mutations were associated with inferior survival [41]. Their data also implied that the survival of the monoallelic cases could be compared with cases of AML stratified as intermediate risk (according to ELN 2017). As more studies need to prove differences in survival, especially in AML cases, further distinction might lead to different therapeutic decisions. However, apart from allelic status, the number of *TP53* mutations are discussed to be relevant for prognosis. The multi-hit cases share poor prognosis regardless of diagnosis of MDS or AML [32, 34]. Multi-hit and biallelic cases are more resistant to standard treatments compared to monoallelic cases [32]. As discussed earlier in the section of AML-MR, the ICC introduced qualifiers, excluding subtypes of secondary and therapy-related AML cases. However, the *TP53* mutation is the most frequent mutation in therapy-related AML [33]. Still, the ICC decided to assess priority to the mutation itself and not ontogeny, most likely due to studies discrediting the relevance of ontogeny [31, 34]. Nonetheless, *Lachowiez* et al. point out that AML-MR cases with MR gene mutations have comparable poor outcome to the AML cases with mutated *TP53* [42]. Lastly, one of the ICC's criteria for AML with mutated *TP53* is pure erythroid leukemia (PEL). Incidentally, in the new WHO classification this disease subtype is included within the AML defined by differentiation entity and is now referred to as acute erythroid leukemia. However, the ICC's authors included this disease subtype to AML with *TP53* mutation, as more than 90% of PEL cases show a minimum of two *TP53* mutations [7, 32]. The criteria for PEL itself is adopted from the former WHO classification [7]. Hypothesising on potential future treatments, immunotherapeutic approaches beyond allo-SCT should be investigated further, since many studies found similarities in immune architecture within *TP53* mutated AML and MDS. [32, 33, 43].

Conclusions

In conclusion, it is important to note that although these two classifications might have different approaches in putting the current state of research into order, they both share the purpose of improving diagnosis and treatment assignment, as Huber et al. report an 86% overlap in diagnosis of their cases [1]. However, it is important to acknowledge the challenge of using input with two classifications in practice. This is particularly true when

defining blast count and the discussed subtypes, including mutated *CEBPA, KMT2A-r* and *MECOM-r*, myelodysplasia-related and mutated *TP53*.

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