Comment on Association of *FLT3*-internal duplication length with overall survival in acute myeloid leukemia: a systematic review and meta-analysis

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults, accounting for 1.3% of new cancer cases, for example in the United States of America and affecting approximately 0.5% of the whole population at any point during their lives.[1] This cancer type is a heterogeneous tumor derived from hematopoietic stem cells with a different profile consisting of cytogenetic, genetic, and epigenetic abnormalities.[2] Genetic analyses, including both karyotyping and screening for recurrent gene fusions and molecular mutations, provide crucial information about its biology.[3] These specific analyses strongly inform prognostic assessment which is used for tailor-made post-remission therapy.[1] Of note, since 2017 an enormous growth has been observed in the number of drugs for the treatment of AML, with several new drugs receiving regulatory approval.[1]

In order to better understand how AML patient survival can be optimized, new risk factors should be included in updated risk assessments tools. This comment focuses on the role of *FLT3*-internal tandem duplication (*FLT3*-ITD) mutations which occur in approximately 25% of adults suffering from AML.[2] As the prognosis of *FLT3*-ITD AML is related to *FLT3*-ITD allelic ratio, length, insertion site, and co-occurring mutations, this genetic aberration was studied by Polak *et al.*[4] In their recent review in *Haematologica*, Polak *et al.* found that there is an association between *FLT3*-ITD length and overall survival (OS). They studied 2,098 *FLT3*-ITD-positive AML patients.[4]

Although the clinical relevance of Polak's study is very clear, some methodological issues can be raised concerning the search strategy used, including the possibility to replicate this search.

First, we are interested in the specifics of the search strategy, foremost when using several databases. In our opinion, it is necessary to show all details of the search strategy used for all consulted databases, so this important topic can be replicated or criticised. It is not uncommon to add search details to the Supplementary Appendix, either within the paper or online only.

Second, more specificically, Polak *et al.* stated that "using all possible spellings of "*FLT3*-ITD" and "Acute Myeloid Leukemia", however this very brief statement doesn't clarify which spelling choices were actually used. It would be very helpful if the authors could provide more details to clarify this part of the text. They might have missed some crucial term variants, or they might have used a term variant with other meanings than the authors would want these terms to have, which might attract non-relevant articles. It would also be very helpful to know which kind of search terms the authors used (controlled vocabulary terms such as MeSH, free text terms, such as words in the abstract or affiliation field).

Third, we have tried to replicate this search with a query of our own making, based on the search the authors described (a combination of three concepts: *FLT3*-ITD, AML and 1996-2021 (details are provided in the *Online Supplementary Appendix*). The results of the replication is as follows: the authors identified 2,010 items in PubMed. With our strategy, we were able to identify 2,348 references in PubMed. This situation is even more telling for Embase and the Cochrane Library. A replication of the search in Embase retrieves 8,689 references (4,051 when excluding meeting abstract references). A more focused search for Embase, which is sometimes applied when the number of results is very high compared to the results in PubMed, retrieves 6,213 references (2,530 when excluding meeting abstracts), approximately 1,000 more than the authors identified. Additionally as we are able to retrieve 306 references from the Cochrane Library (130 when excluding meeting abstract references) it could well be that the authors' strategy for the Cochrane Library was technically imperfect, as they retrieved no references from this source (the Cochrane Library interface at Wiley Online is very sensitive for double spaces or hyphens). Finally, adding other potential relevant sources might increase the number of results even further e.g., searching for this topic in Web of Science retrieves 3,127 references (2,697 when excluding meeting abstract references). We think that Polak *et al.* might have missed relevant references. It could be that some relevant terms were missed by the authors. We would like to suggest that this should also be clarified by the authors.

To conclude, the authors should be acknowledged for their extensive attempt to study the role *FLT3*-ITD length in AML patients in this large meta-analysis. This is a significant clinical genetic aberration which was addressed by Polak *et al.* However, the literature search methodology is unclear. Adding all search details will aid

in better understanding of the prognostic value of this aberration and potential new ones to update risk stratification protocols for AML in the upcoming years.

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https://doi.org/10.3324/haematol.2022.281908

Received: September 1, 2022.
Accepted: September 9, 2022.
Early view: October 6, 2022.

Disclosures

No conflicts of interest to disclose.

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