Peer Review File

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Reviewer Comments

The manuscript studies published gene expression data of AML patients to investigate cuproptosis-related genes. While the methods are scientifically sound, the results add little to the field of AML research. Questions on the pathophysiological relevance of the findings are rather raised than answered. The differential expression of cuproptosis-related genes is nicely described. The prognostic model ignores major established prognostic factors and need thorough revision.

Major points:

•**Comment 1:** The prognostic model includes (in addition to the new cuproptosis-related gene score) age, sex, and tumor mutation burden (TMB). TMB is not a clinically relevant genetic risk factor in AML. In contrast, specific genetic aberrations are used for genetic risk stratification in AML (e.g. ELN risk groups, see PMID: 35797463). The development of a prognostic model that ignores well established risk scores is not meaningful. This part needs a thorough revision of the model replacing TMB by established genetic risk stratification in AML.

Reply: Comments are gratefully acknowledged. This study was primarily based on sequencing data from AML and normal samples in the TCGA and GTEx public databases to explore the relationship between copper death and AML. A bioinformatic approach was used to initially obtain 2 copper death-related genes (PACS2 and NDUFV1) associated with AML prognosis and construct risk models to predict survival time of patients. As the TCGA-AML and GSE37642 databases did not contain information such as clinical characteristics associated with ELN classification and genetic risk factors, the relationship between our constructed risk models and ELN classification could not be explored and clinical information of AML samples was added to TableS10 :The clinical information of AML samples in the TCGA and GTEx database. However, we will subsequently collect a large number of clinical samples to further validate our risk model for copper mortality and will explore the relationship between the risk model and ELN classification and the influence of other genetic-related factors as suggested by you.

Minor points:

•**Comment 2:** References on general background are outdated. E.g. 3) ELN 2010 neglects ELN 2017 and ELN 2022 recommendations. In line, recent developments in AML therapy are neglected in the introduction.

Reply: Thank you for your comments. In response to your suggestion we have added relevant background information to the introduction of the manuscript, which reads:

“For patients suitable for intense chemotherapy, the standard dose anthracycline and cytarabine "3+7" regimen remains the first-line option. However, for patients who are not candidates for intense chemotherapy, the combination of vinecla with a demethylating agent (HMA) or a low dose of cytarabine is now the standard regimen”(see Page 4, line 51)

•**Comment 3：** The abstracts lacks some background information. The corresponding paragraph just consist of the aim of the study.

Reply: Comments are gratefully acknowledged. In response to your suggestion we have added relevant background information to the abstract section of the manuscript, which reads: “Acute myeloid leukemia (AML), a common form of acute leukemia, is due to tumor changes and clonal proliferation caused by genetic variants. Cuproptosis is a novel form of regulated cell death”(see Page 2, line 20).

•**Comment 4：** Some points of the discussion are overexaggerated. E.g. line 269 “to provide a reference for clinical screening of AML and targeted therapy measures.” is not in the least supported by the data.

Reply: We apologize for our error. At your suggestion we have amended the sentence as follows: Therefore, we constructed a risk model for AML based on CRG and analyzed its correlation with immune infiltration, which will provide a theoretical basis for studying the relationship between cuproptosis and AML(see Page 13,line 232).