DOI: https://doi.org/10.61841/df08k472 Publication URL: https://nnpub.org/index.php/MHS/article/view/2223

PROGNOSTIC MODELS FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A TEN-YEAR SYSTEMATIC REVIEW

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ABSTRACT

Background: *CLL is the most common malignant neoplasm of aging adults in Western populations. CLL is a hematology malignancy defined by the continuous proliferation of monoclonal B lymphocytes in bone marrow, peripheral blood, and lymphoid organs that have a specific immunophenotype. Clinical outcomes for patients with CLL are heterogeneous, leading to the development of prognostic factors. CLL-IPI is a commonly used tool for predicting outcomes.*

The aim: *This study aims to determine the prognostic models for CLL.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SAGEPUB, and ScienceDirect, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Results: *In the PubMed database, the results of our search brought up 27 articles, whereas the results of our search on SAGEPUB brought up 415 articles, our search on ScienceDirect brought up 742 articles. In the end, we included four research that met the criteria.*

Conclusion: *In conclusion, of the five models, the CLL-IPI shows the best predictive performances. However, further research is needed.*

Keywords: *Prognostic models, CLL, predictive performances*

INTRODUCTION

Chronic lymphocytic leukemia is the most common malignant neoplasm of aging adults in Western populations.[1–3] CLL is a hematology malignancy defined by the continuous proliferation of monoclonal B lymphocytes in bone marrow, peripheral blood, and lymphoid organs that have a specific immunophenotype (e.g. CD5, CD19, CD20, and CD23).[4,5] CLL is the most common adult leukemia in the Western World, accounting for 25% of all leukemias and 1.3% of all cancers. It is more prevalent among Asians and Ashkenazi Jews. The American Cancer Society predicts 21,040 new CLL cases and 4,060 deaths in 2020, with 191,000 cases and 61,000 deaths worldwide. CLL affects adults as young as 30 and is rare in children. The incidence increases with age. CLL predominantly affects older individuals, with males and whites more frequently affected than other races.[1,6]

CLL diagnosis requires 5 x 10^9/L B lymphocytes in peripheral blood and a clonal B-cell population, detected by flow cytometry, positive for light chain restriction, CD5, CD23, CD79b, surface immunoglobulin expression, and low CD20 levels. CLL cells have a typical appearance of smudge cells. Small lymphocytic lymphoma is a clinical variant of the same histopathologic entity when a clonal B-cell population is detected in enlarged lymph nodes without peripheral clonal lymphocytes.[6]

Indication for treatment patients with CLL according to the 2008 iwCLL based on 3 factors that were constitutional symptoms, complete blood cell count, and physical examination findings. The treatment indications were progressive constitutional symptoms (persistent, inexplicable fever (temperature more than 38 °C) and/or weight loss (more than 10% of baseline weight lost in less than six months) and/or intense sweating at night), progressive bone marrow failure: anemia and/or thrombocytopenia, progressive lymphadenopathies (at least 10 cm), progressive hepatomegaly or splenomegaly, progressive lymphocytosis (doubling times <6 months), steroid-refractory autoimmune hemolytic anemia and/or immune thrombocytopenia.[6] The initial choice of treatment depends on the symptoms and genetic risk stratification. The treatment options are targeted agents (Bruton tyrosine kinase (BTK) inhibitors), and chemoimmunotherapy (fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine plus rituximab (BR)).[1]

Clinical outcomes for patients with CLL are heterogeneous, leading to the development of prognostic factors. Rai and Binet developed two staging systems over four decades ago, based on simple clinical parameters like blood cell count and physical examination. The five stages identified by Rai and the three stages by Binet are associated with differential outcomes. CLL patients have a median survival of 10 years, with Rai stage 0-II patients potentially surviving 5-20 years without treatment. The International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI) is a commonly used tool for predicting outcomes.[1]
The purpose of this study is to determine the prognostic models for CLL.

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this systematic review, we compare and contrast the prognostic models for CLL. It is possible to accomplish this by researching or investigating the prognostic models that predict overall survival and treatment-free survival. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

For researchers to take part in the study, they needed to fulfill the following requirements: 1) The paper needs to be written in English, and it needs to investigate the prognostic models for CLL. For the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "prognostic models"; "CLL"; and "predictive performances" as keywords. The search for studies to be included in the systematic review was carried out in March, 16th 2024 using the PubMed, SAGEPUB, and ScienceDirect databases by inputting the words: (("prognostic"[All Fields] OR "prognostical"[All Fields] OR "prognostically"[All Fields] OR "prognosticate"[All Fields] OR "prognosticated"[All Fields] OR "prognosticates"[All Fields] OR "prognosticating"[All Fields] OR "prognostication"[All Fields] OR "prognostications"[All Fields] OR "prognosticator"[All Fields] OR "prognosticators"[All Fields] OR "prognostics"[All Fields]) AND ("model"[All Fields] OR "model s"[All Fields] OR "modeled"[All Fields] OR "modeler"[All Fields] OR "modeler s"[All Fields] OR "modelers"[All Fields] OR "modeling"[All Fields] OR "modelings"[All Fields] OR "modelization"[All Fields] OR "modelizations"[All Fields] OR "modelize"[All Fields] OR "modelized"[All Fields] OR "modelled"[All Fields] OR "modeller"[All Fields] OR

"modellers"[All Fields] OR "modelling"[All Fields] OR "modellings"[All Fields] OR "models"[All Fields]) AND "CLL"[All Fields] AND (("predict"[All Fields] OR "predictabilities"[All Fields] OR "predictability"[All Fields] OR "predictable"[All Fields] OR "predictably"[All Fields] OR "predicted"[All Fields] OR "predicting"[All Fields] OR "prediction"[All Fields] OR "predictions"[All Fields] OR "predictive"[All Fields] OR "predictively"[All Fields] OR "predictiveness"[All Fields] OR "predictives"[All Fields] OR "predictivities"[All Fields] OR "predictivity"[All Fields] OR "predicts"[All Fields]) AND ("perform"[All Fields] OR "performable"[All Fields] OR "performance"[All Fields] OR "performance s"[All Fields] OR "performances"[All Fields] OR "performative"[All Fields] OR "performatively"[All Fields] OR "performatives"[All Fields] OR "performativities"[All Fields] OR "performativity"[All Fields] OR "performed"[All Fields] OR "performer"[All Fields] OR "performer s"[All Fields] OR "performers"[All Fields] OR "performing"[All Fields] OR "performs"[All Fields]))) AND ((y_10[Filter]) AND (english[Filter])) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers examined to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilize as sources for their article and selected those studies. After looking at several different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't be seen anywhere else.

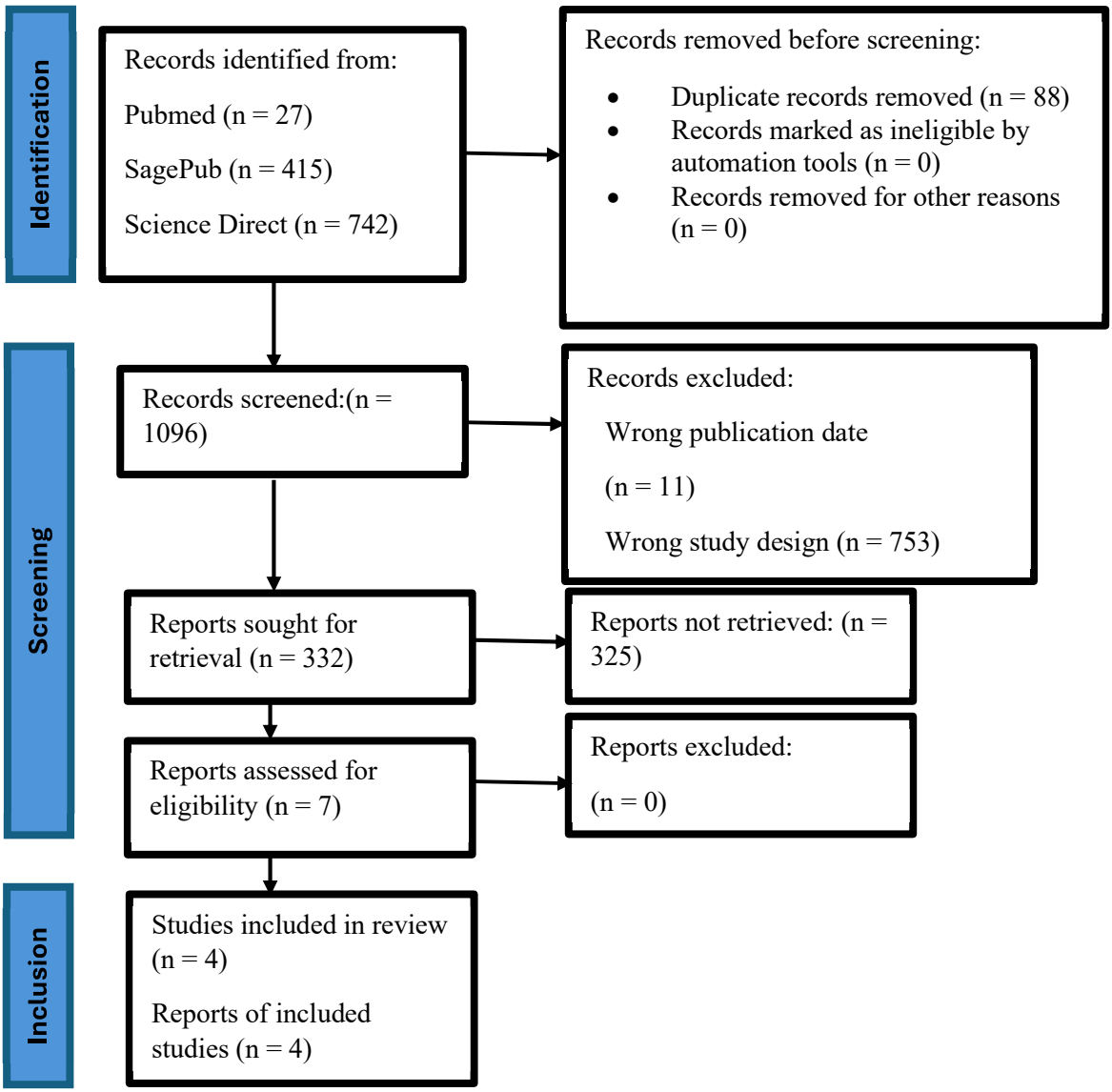

Figure 1. Prisma Flow Diagram

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed

in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before deciding on which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criterion is utilized in the process of selecting papers for further assessment to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 27 articles, whereas the results of our search on SAGEPUB brought up 415 articles, our search on ScienceDirect brought up 742 articles. In the end, we included four research that met the criteria.

CLL International Prognostic Index (CLL-IPI)

This score includes five prognostic factors: age, clinical stage, IgHV mutational status, B2-microglobulin and TP53 status. Muñoz-Novas, et al. (2018)[7] showed that in terms of OS prediction, the model turned out to be statistically significant. There were notable variations in the 5-year survival probability among the risk groups as well. Median OS (95% CI) and 5-year OS in low risk, intermediate risk median, High risk, and Very high risk groups were 238.5 (147–330) and 93.6; 144.8 (127.8–161.8) and 87.6; 73.7 (56.6–90.7) and 67.8; 31.8 (21.2–42.4) and 28.6, respectively (<0.0001).

Ferroptosis- related prognostic score

Pan, et al. (2022)[8] suggested in order to stratify patients into low- and high-risk groups, we built a unique ferroptosis-related prognostic score (FPS) model using nine FRGs (AKR1C3, BECN1, CAV1, CDKN2A, CXCL2, JDP2, SIRT1, SLC1A5, and SP1). According to a Kaplan–Meier analysis, patients with high FPS had lower treatment-free survival (TFS) and overall survival (OS) (P<0.0001), respectively. ROC curves assessed the FPS model's prognostic prediction capability. Furthermore, in CLL patients, there was a correlation found between the risk scores and immune-related pathways and cell types. The findings in the validation cohort validated the association between the high-risk group and poorer OS (P<0.0001), progress-free survival (PFS) (P=0.0140), and TFS (P=0.0072).

Ferroptosis-related lncRNAs prognostic score (FPS)

Xu, et al. (2023)[9] showed that a novel ferroptosis-related lncRNAs prognostic score (FPS) model includes six FRLs: PRKCQ, TRG.AS1, LNC00467, LNC01096, PCAT6, and SBF2.AS1. According to the findings of this study, patients in the high-risk group fared worse in terms of survival than those in the low-risk group. The chemokine signaling system, hematopoietic cell lineage, T cell differentiation, TCR pathway, and NF-κB pathway were shown to have higher levels of enrichment for the differently expressed genes (DEGs) between the two groups, according to functional enrichment analyses. Furthermore, notable variations in immune cell infiltration were also noted. It was discovered that FPS was a reliable independent prognostic predictor for OS.

Barcelona-Brno score

This score includes three prognostic factors: IgHV mutational status, del(17p) and del(11q). Muñoz-Novas, et al (2018)[7] showed that the probability of OS showed significant differences between risk groups. Median OS (95% CI) and 5-year OS in low risk, intermediate risk median, and high risk groups were 238.5 (146.8–330) and 90.7; 131.9 (95–167.9) and 81.4; not reached and 66.2; respectively (p <0.0001)

Super-Enhancer–Associated nine-gene prognostic score

A super-enhancer (SE) is a cluster of enhancers involved in cell differentiation and tumorigenesis, and is one of the promising therapeutic targets for cancer therapy in recent years. In Liang et. al, (2022)[10] showed that LASSO-penalized Cox regression analysis was used to screen a nine-gene prognostic model, which includes TCF7, VEGFA, MNT, GMIP, SLAMF1, TNFRSF25, GRWD1, SLC6AC, and LAG3, using the CLL-related super-enhancers in the training database. After more construction of the SE-related risk score, it was discovered that the prediction performance with respect to overall survival and time-to-treatment (TTT) was acceptable.

Table 1. The literature included in this study

Author	Origin	Method	Sample Size	Result
Liang, 2022[10]	China	NA	Dataset of 107 patients	This finding suggested a helpful predictive score for OS in patients with untreated CLL was introduced, and it can be calculated by measuring the expression levels of nine different genes. In a standard diagnostic, it might also be completed quickly. These nine SE-associated genes in this model were essential for the onset and course of CLL, and they may also help direct the creation of substitute treatments.
Muñoz-Novas, 2018[7]	Spain	Cohort	Data of 696 patients	The results showed that MD Anderson Cancer Center prognostic index (MDACC PI), the CLL-international prognostic index (CLL-IPI), and the Barcelona-Brno biomarkers have a strong capacity to forecast the clinical trajectory of individuals with CLL.
Pan, 2022[8]	China	Cohort	Data of 36 patients	For prognostic prediction in CLL, a unique ferroptosis-related prognostic score (FPS) model can be applied. The model index might also make it easier to create novel clinical treatments for CLL patients that target ferroptosis.
Xu, 2023[9]	China	NA	Data of 151 patients	In order to reliably predict prognosis and characterize the unique immune infiltrate in CLL, we developed and assessed a novel prognostic risk model with six ferroptosis-related lncRNAs (FRLs).

DISCUSSION

Chronic lymphocytic leukemia (CLL) also known as small lymphocytic lymphoma (SLL) is characterized by the proliferation and accumulation of mature but dysfunctional, CD5-positive B-cells in various body parts, including the blood, bone marrow, lymph nodes, and spleen. The development of new diagnostic and prognostic tools for CLL resulted from the significant knowledge of the pathogenesis of this disease.[1,11] For patients with Chronic Lymphocytic Leukemia (CLL), lymphocyte doubling time is a predictive factor; untreated patients exhibit more severe expression. A mutant Ig

heavy chain variable region, a 13 q deletion, low ZAP-70 expression, and low CD38 levels are all favorable prognostic markers. High-risk cytogenetic abnormalities are among the unfavorable variables. The prognosis is poorer for patients with thrombocytopenia, hepatosplenomegaly, multiple-chain lymphadenopathy, and anemia.[1]

Several biological and genetic indicators have been identified that have a significant prognostic impact on CLL patients. These markers include chromosomal abnormalities (deletion 13q, deletion 17p, deletion 11q, trisomy 12), TP53 mutational status, and immunoglobulin heavy variable (IGHV) genes. Leukemogenesis is triggered by the loss of miRNAs (miR-15a and miR-16-1), which is caused by deletion13q. The ATM gene, which codes for the DNA damage response kinase ATM, is lost due to deletion 11q. TP53, the tumor suppressor gene, is usually deleted by deletion 17p. The remaining TP53 allele is mutated, which disrupts the TP53 pathway functionally. Thus, deletion 17p and TP53 mutations are grouped as genetic TP53 aberrations. Further recurrent mutations in NOTCH1, XPO1, KLHL6, MYD88, and SF3B1 somatic genes have been found.[11,12]

A prognostic model is a mathematical function that estimates a patient's probability of experiencing a specific health event within a defined time frame using at least two prognostic factors. Prognostic factors, such as individual or disease characteristics like age, gender, disease stage, or genetic information, can predict patient-relevant outcomes like overall survival or disease progression. Recent years have identified several clinical and biological prognostic factors for CLL, including serum markers, genomic aberrations, gene abnormalities, mutation status of IgHV segments, non-coding RNA, and surrogate markers (immunophenotypic) like CD38 and ZAP-70 expression.[2,13] For CLL patients, there are two staging schemes in use. There are two staging systems for CLL patients, that is the modified Rai-Sawistsky in the United States and Binet staging in Europe.[1]

Serum markers CLL which is lymphocyte doubling time (LDT), serum thymidine kinase (s-TK), serum beta2-microglobulin (s-ß2M), and lactic dehydrogenase (LDH) predict poor prognosis. Long treatment-free duration and survival are linked to LDT > 12 months, while LDT < 12 months indicates a poor prognosis. S-β2M and S-TK levels are independent indicators of progression-free survival (PFS) in CLL. Elevated s-TK levels indicate high risk and predict disease course. LDH indicates time to first treatment (TTFT), Richter's transformation, overall survival (OS), and shorter PFS. LDH also has predictive significance for trisomy 12 patients.[13] The interval between the date of diagnosis and the start of treatment or the last follow-up at which the patient was known to be untreated was called the time to first treatment (TTFT).[14] The LDT in CLL indicates the rate of neoplastic lymphocyte accumulation in the body as well as its speed of birth. OS is correlated with LDT, an independent biomarker that has been validated.[15]

CD38 and ZAP70 expression are validated as prognostic indicators for CLL, predicting TTFT in the Binet 0 stage. CD38 positivity predicts treatment resistance, hepatomegaly, and shorter survival. ZAP70 expression predicts disease progression and Ritcher's syndrome. CD38 positive identifies unmutated IGHV clones, while ZAP70 indicates IGHV mutation status.[13]

There are several prognostic tools for CLL such as the CLL International Prognostic Index (CLL-IPI), the MDACC 2007 index score, and the Barcelona-Brno score. When it came to predicting who would live longer with CLL and who would live shorter, the CLL-IPI performed the best.[2]

CLL-IPI is classified into 4 subgroups: low risk (0-1) points, intermediate risk (2-3) points, high risk (4-6) points, and very high risk (7-10) points. The parameters were TP53 status (i.e. del17p or TP53 mutation) for 4 points, IGHV mutational status (unmutated IGHV), and serum ß2-microglobulin >3.5 mg/L for 2 points, age >65 years and advanced clinical stage (Rai I-IV or Binet B-C) for 1 point.[7,16]

The total number of points allocated to each of the six prognostic indicators was used to classify patients into one of the three risk groups suggested by the MDACC: low risk (1-3 points), intermediate risk (4–7 points), or high risk (≥8 points). Ages <50 years, male sex, β2-microglobulin levels 1-2x upper limits of normality, absolute lymphocyte counts of 20–50 × 109/L, Rai stages III or IV, and at least three nodal regions affected were all given one point each. Ages between 50 and 65, β2-microglobulin levels >2x upper limits of normality, and absolute lymphocyte counts >50 × 109/L were given two points, and ages >65 years received three points.[7]

Pflug et al. (2014) study showed that sex, age, ECOG PS (Eastern Cooperative Oncology Group Performance Status), genetic aberrations del17p and del11q, IGHV MS, s-TK, and s-ß were significant as independent predictors of overall survival patients CLL[17] This study supports our findings study of Muñoz-Novas, et al. (2018)[7] prognostic factors that significant related to OS.

Patients Rani et al. (2018) study were risk stratified as per CLL-IPI, Barcelona-Brno index, M. D. Anderson Cancer Center (MDACC), O-CLLI score, and modified GCLLSG index. In this study, univariate analysis of nine parameters including gender, lymph node groups, absolute lymphocyte count (ALC), ECOG PS, age, Rai stage, copy number variations, β2M, and IGHV mutational status, all parameters except gender and age were statistically significantly associated with OS and TTFT. This study also showed that on multivariate analysis IGHV mutational status, β2M, and performance status have independent prognostic linked with TTFT, while Rai stage, del(17p), and IGHV mutational status retained independent

prognostic linked with OS. 86 individuals died away throughout the research period, 78 of them as a result of their condition getting worse.[18]

A study by Gentile et al. (2018) used two prognostic models that were CLL-IPI and the Barcelona Brno prognostic model. All the selected markers for the CLL-IPI score which is del17p, IGHV mutational status, ß2M plasma concentration, clinical stage, and age led to the identification of four patient subsets (low-, intermediate-, high-, and very high-risk) showed an independent prognostic impact on OS. Also, all parameters of the Barcelona-Brno prognostic model (IGHV mutational status, del17p, and del11q) of this study showed an independent predictive power on survival. This study confirms the usefulness of the CLL-IPI score in predicting the survival of CLL patients who have not yet received treatment. Furthermore, in this study group, the CLL-IPI score appears to be a more accurate predictor of progression than the Barcelona-Brno prognostic model.[19]

CONCLUSION

In conclusion, of the five models, the CLL-IPI shows the best predictive performances. However, further research is needed.

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