

RESEARCH ARTICLE

Preoperative platelet lymphocyte ratio as independent predictors of prognosis in pancreatic cancer: A systematic review and meta-analysis

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Abstract

Background

Recently, the preoperative platelet to lymphocyte ratio (PLR) has been found reported to predict oncologic outcomes in multiple malignancies. However, its prognostic value in patients with pancreatic cancer (PC) remains controversial. The aim of this study was to assess the prognostic value of preoperative PLR in PC.

Methods

MEDLINE, EMBASE, and Cochrane databases were searched to identify studies evaluating the prognostic significance of preoperative PLR in PC. Pooled hazard ratios (HRs) for overall survival (OS) were calculated using fixed-effects/random-effects models.

Results

A total of eight studies comprising 1,904 patients with PC were included in the meta-analysis. The pooled analysis demonstrated that elevated PLR had an association with decreased OS (HR: 1.22, 95% CI: 1.04–1.43, $p = 0.02$). Subgroup analysis showed that a high PLR significantly predicted poor OS in Asian studies (HR: 1.25, 95% CI: 1.03–1.52, $p = 0.02$), patients with metastatic disease (HR: 1.34, 95% CI: 1.01–1.77, $p = 0.04$) and patients with PLR >150 (HR: 1.73, 95% CI: 1.21–2.49, $p = 0.003$).

Conclusions

The preoperative PLR may be a significant independent prognostic factor in patients with PC.

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Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death worldwide [1]. Radical resection without residual tumor is the most effective therapy for the majority of patients. Nevertheless, more than 80% of patients are diagnosed at inoperable late stages [2], and the prognosis is extremely poor. Data from the Surveillance, epidemiology and End Results (SEER) database (2006–2012) demonstrates that the 5-year survival of patients with pancreatic cancer is 7.7%. Therefore, identifying a predictive biomarker that could be used to determine individualize therapy and to predict prognosis remains important.

Host inflammatory responses can largely influence tumor development and progression [3]. Several inflammatory factors, such as plasma fibrinogen, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR) are identified as useful indicators for predicting the prognosis in renal cell carcinoma, ovarian cancer, and hepatocellular carcinoma [4–6]. Recently, the preoperative platelet to lymphocyte ratio (PLR), which also reflects the degree of systemic inflammation, has been found to be linked to prognosis in patients with PC [7–9]. However, some studies failed to find correlation between PLR and prognosis of PC [10–12]. We therefore conducted a meta-analysis to assess the prognostic effect of preoperative PLR in PC.

Materials and methods

Search strategies

The present study was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines [13]. We searched MEDLINE, EMBASE, Cochrane databases from inception up to August 2016. The following search terms were used: “pancreatic cancer” or “pancreatic ductal adenocarcinoma”, “platelet to lymphocyte ratio” or “PLR” or “platelet lymphocyte ratio” or “platelet-lymphocyte ratio”, “prognostic” or “prognosis” or “survival” or “outcome”. In addition, manual searches were performed in the web and by reviewing the citation lists of the retrieved articles. However, we did not search the grey literature. Detailed search strategies refer to [S2 File](#).

Study selection

The criteria for inclusion were listed as follows: (1) PC was pathologically confirmed; (2) assessing the prognostic value of preoperative PLR on OS; (3) studies supplied sufficient information for calculating hazard ratio (HR) and 95% confidence interval (CI); and (4) reporting a dichotomous cut-off value for PLR. The exclusion criteria were as follows: (1) reviews, letters, case-reports, and conference abstracts without original data; (2) overlapping or duplicate data; and (3) non-English language studies.

Data extraction

The two reviewers independently reviewed all eligible studies and extracted data. Any disagreement was resolved by discussions among all coauthors. The following information was collected: first author’s name, year of publication, country, number of patients, region of publication, tumor stage, overall survival (OS), survival analysis methods, cut-off values, and time of follow-up. HRs were extracted from multivariate or univariate analyses or estimated from Kaplan-Meier survival curves [14].

Quality assessment

The quality of each study was assessed in accordance with the Newcastle-Ottawa Scale (NOS) [15], which included an assessment of subject selection, comparability of groups, and clinical outcome. A total of nine items were extracted, and each item scored 1. The total scores ranged from 0 to 9. If scores are ≥ 7 , the study is considered as high quality.

Statistical analyses

The meta-analysis was conducted by STATA 12.0 (College Station, TX, USA). Heterogeneity of the HR of each study was quantified using Cochran's Q test and Higgins- I^2 statistic. A p-value < 0.1 for the Q-test or $I^2 > 50\%$ was considered statistically significant. A random effect model was used if heterogeneity was observed, while a fixed effect model was applied in the absence of inter-study heterogeneity. HRs and corresponding 95% CIs were directly extracted from the published data or calculated using previously published methods proposed by Tierney et al. [16]. Subgroup analyses were conducted based on the region of publication, tumor stage, treatment method, NOS score, and the cut-off value of PLR. Sensitivity analyses were carried out to evaluate result stability excluding each study. If the number of included studies was more than 11, the publication bias was evaluated using funnel plots and with the Begg's funnel plots and Egger's tests [17, 18]. $P < 0.05$ was considered statistically significant.

Results

Search results

Our search strategy yielded 63 potentially relevant articles. After removing duplicates, 56 articles remained to be screened. Of these, 34 were excluded through titles and abstracts, leaving 22 articles for detailed evaluation. As a result, 8 eligible studies, comprising a total of 1,904 patients, were included in the quantitative synthesis. The selection process was shown in Fig 1.

Characteristics of the included studies

Most of these studies have been published since 2014. The sample sizes ranged from 110 to 440. Six studies reported on Asians, and two study on Europeans. HRs and 95% CI were extracted directly from the seven studies. HRs in one study were estimated by Kaplan-Meier survival curves. The cut-off values for PLR ranged from 126 to 225, two studies used a PLR cut-off value ≥ 150 , while six studies used a PLR < 150 . In methodological quality of studies, the overall NOS scores ranged 6 to 8, with a median of 6.8. Table 1 lists the detailed study characteristics.

Meta-analysis

Overall survival. A total of 1,904 patients from eight studies were included in the analysis of HRs for OS. The pooled analysis demonstrated that elevated PLR had an association with decreased OS (HR: 1.22, 95% CI: 1.04–1.43, $p = 0.02$). However, excessive heterogeneity existed between studies ($p = 0.001$, $I^2 = 70\%$). Thus, the random-effects model was used (Fig 2).

To detect the potential heterogeneity, subgroup analyses stratified by region of publication, treatment, disease stage, NOS score, and the cut-off value of PLR (Table 2). Exploratory subgroup analysis according to region of publication showed that high PLR predicted worse OS in Asian studies (HR: 1.25, 95% CI: 1.03–1.52, $p = 0.02$). When stratified by treatment methods, high PLR did not have prognostic effect in all subgroups. Pooled HRs for OS stratified by disease stage, elevated PLR predicted decreased OS in patients with metastatic disease (HR: 1.34,

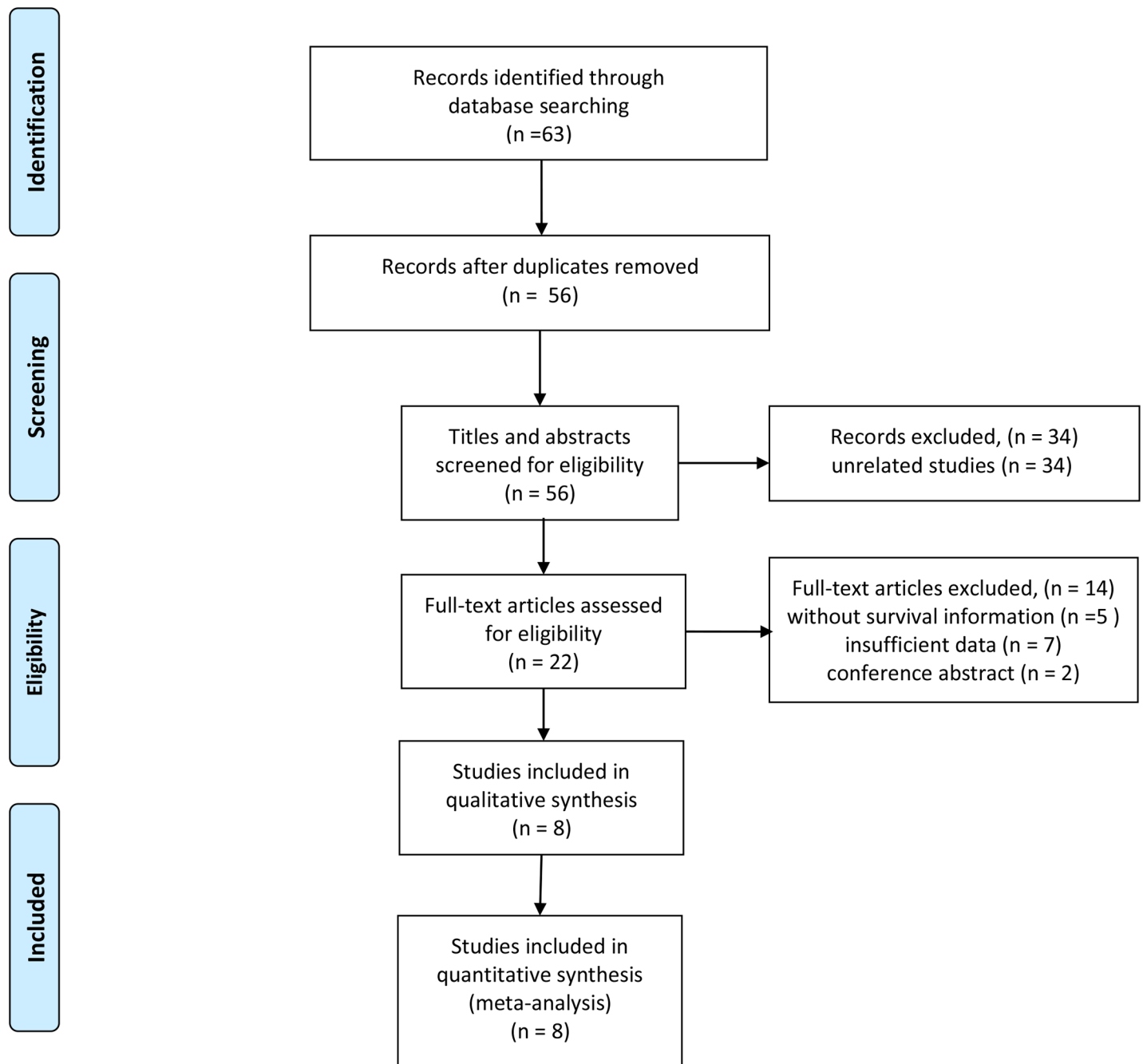


Fig 1. Flow diagram of the study selection process.

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95% CI: 1.01–1.77, $p = 0.04$). The cut-off values ranged from 126 to 225. We stratified cut-off values into two subgroups: ≤ 150 and > 150 . Stratification by the cut-off value found that patients with $PLR > 150$ had significantly worse OS (HR: 1.73, 95% CI: 1.21–2.49, $p = 0.003$), however, the prognostic effect disappeared in patients with $PLR \leq 150$ (HR: 1.13, 95% CI: 0.99–1.30, $p = 0.08$). Subgroup analysis according to NOS score found that the prognostic role of PLR was observed in studies with NOS score ≥ 7 (HR = 1.18; 95% CI = 1.04–1.33; $P = 0.008$), however, when NOS score < 7 , the prognostic efficiency disappeared in the pooled

Table 1. Characteristics of the studies included in the meta-analysis.

Author	Year	Country	Region	Follow-up (months)	Treatment	No. of patients	Stage	Cut-off value	Survival analysis	Analysis	NOS score
Shirai	2015	Japan	Asia	NA	Surgery	150	No-metastatic	150	OS	MV/UV	6
Smith	2009	UK	Europe	12(7.8–25.5)	Surgery	110	No-metastatic	150	OS	MV	6
Qi	2015	China	Asia	NA	Chemotherapy	211	Metastatic	126	OS	MV/UV	7
Martin	2014	Austria	Europe	12	Mixed	124	Metastatic	200	OS	MV/UV	8
Kou	2016	Japan	Asia	10.8(1.7–72.1)	Chemotherapy	306	Metastatic	150	OS	UV	7
Lnoue	2014	Japan	Asia	18.7(6.1–68.2)	Mixed	440	Mixed	150	OS	MV/UV	8
Asari	2016	Japan	Asia	18(10–35)	Surgery	184	Mixed	225	OS	MV/UV	6
Yamada	2016	Japan	Asia	15.1(0.43–150.7)	Surgery	379	Mixed	150	OS	MV/UV	8

OS: overall survival; MV: multivariate; UV: univariate; NA: not available

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results. In order to assess the influence of single studies on the overall estimate, the sensitivity analysis was performed. Each single study was removed each time to estimate the influence of individual data sets on the combined HR for OS. The results showed that no study had a significant effect on the observed effect size (pooled HR), indicating the robustness of our findings.

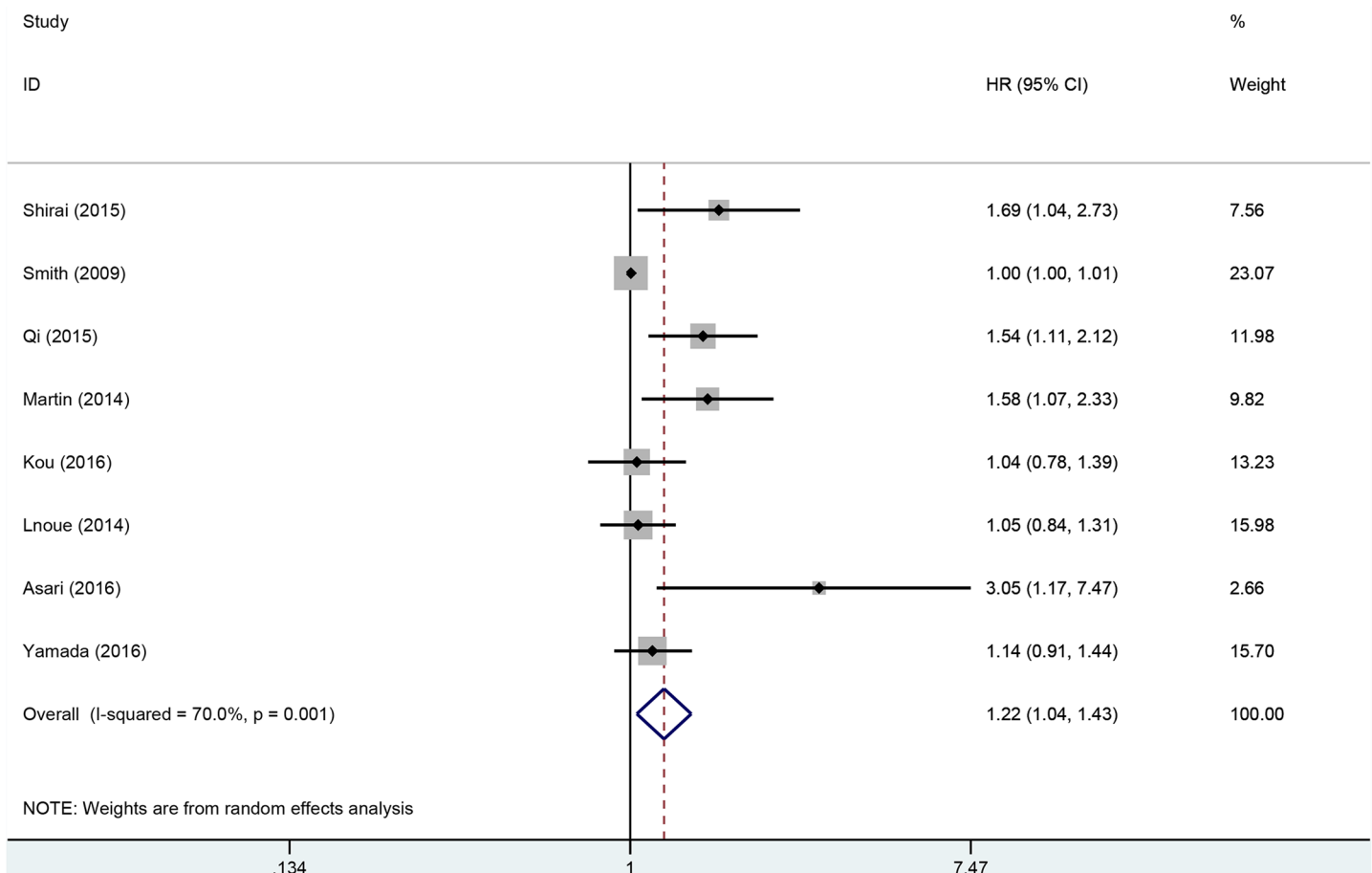


Fig 2. Forest plots for the association between PLR and OS.

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Table 2. Pooled hazard ratios (HRs) for OS according to subgroup analyses.

Subgroup	No. of studies	No. of patients	Effects model	HR (95% CI)	P value	Heterogeneity	
						I ² (%)	P _n
Overall	8	1,904	Random	1.22 (1.04–1.43)	0.02	70	0.001
Region							
Asia	6	1,670	Random	1.25 (1.03–1.52)	0.02	53	0.06
Europe	2	234	Random	1.21 (0.78–1.87)	0.40	80.8	0.02
Treatment							
Surgery	4	823	Random	1.24 (0.95–1.62)	0.11	73.2	0.01
Chemotherapy	2	517	Random	1.26 (0.86–1.84)	0.24	68	0.08
Mixed	2	564	Random	1.25 (0.84–1.85)	0.28	68.9	0.07
Disease stage							
No-metastatic	2	260	Random	1.23 (0.75–2.02)	0.42	77.8	0.03
Mixed (non-metastatic & metastatic)	3	1,003	Random	1.19 (0.89–1.60)	0.24	58.7	0.09
Metastatic	3	641	Random	1.34 (1.01–1.77)	0.04	53.4	0.12
Cut-off for PLR							
>150	2	308	Fixed	1.73 (1.21–2.49)	0.003	36	0.21
≤150	6	1,596	Random	1.13 (0.99–1.30)	0.08	60	0.03
NOS score							
<7	3	444	Random	1.50 (0.85–2.64)	0.16	79	0.008
≥7	5	1460	Fixed	1.18 (1.04–1.33)	0.008	40	0.16

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Discussion

In the present study, we identified 8 studies involving 1,904 patients that investigate the prognostic value of preoperative PLR in patients with PC. This meta-analysis showed that elevated PLR is an independent predictor of worse OS in patients with PC. Furthermore, subgroup analysis showed that the adverse prognostic effect of high PLR remained substantial in Asian studies, patients with metastatic disease and patients with PLR >150, as well as for studies with NOS score ≥7. These findings suggest PLR was predictive of OS. It may provide important supporting information to inform treatment decisions and predict treatment outcomes. For example, clinicians may use different treatment strategies for high-risk patients, such as changes in the inflammatory response, regulation of the immune system, and neoadjuvant chemotherapy, etc. Therefore, the individualized treatment may improve the prognosis of patients with PC.

The actual mechanisms between high PLR and poor outcome of PC are unclear. It has been suggested that cross-talk exists between the inflammatory response and tumor progression [3, 19, 20]. Cancer-related inflammation could suppress antitumor immunity by recruiting immunosuppressive cells such as regulatory T cells and myeloid-derived suppressor cells (MDSC), resulting in tumor progression [21, 22]. Platelet, as a critical source of cytokines, binds directly to members of the VEGF, PDGF, FGF, and TGF-β, thus the platelet acts as a reservoir for secreted growth factors that regulate tumor angiogenesis, cell proliferation, migration, and metastasis [23–25]. Lymphocytes play a critical role in the cell-mediated antitumor immune response. The lymphocyte count reflects the degree of responsiveness of the immune system of the host [26, 27]. Tumor-infiltrating lymphocytes (TILs) are important immune cells found in tumor and responsible for antitumor immune responses [28]. In addition, low lymphocyte counts are thought to be responsible for an insufficient immunological response,

which leads to inferior survival in multiple cancers [29, 30]. Taken together, PLR combined with the effects of platelet and lymphocyte may predict the prognosis of patients with PC.

Nevertheless, our study has several limitations. First, excessive heterogeneity existed among studies. Subgroup analyses didn't find the potential sources of heterogeneity. In addition, we performed sensitivity analysis. The results showed that no study had a significant effect on the observed effect size (pooled HR). Second, the cut-off value for PLR differed in each study. This might be significant contributors to substantial heterogeneity. Third, HRs and their 95% CIs were extracted from univariable analyses in one study and estimated from Kaplan-Meier survival curve in one study. Thus, the prognostic role of PLR might be overestimated. Fourth, all included studies were retrospective, which was more susceptible to some biases. Fifth, although the p values are significant, the 95% CIs for HR for elevated PLR and OS (1.04–1.43), Asian studies (1.03–1.52) and patients with metastatic disease (1.01–1.77) are very close to 1. Given that this is a meta-analysis with a large sample size, and as a result powered to detect small differences, the clinical relevance are of questionable significance.

In conclusion, our findings demonstrated that the preoperative PLR may be a significant independent prognostic factor in patients with PC. However, considering the limitations listed above, future high-quality studies are warranted to further determine the prognostic value of PLR in patients with PC.

Supporting information

S1 File. PRISMA 2009 checklist in this meta-analysis.

(DOC)

S2 File. Search strategies of this meta-analysis.

(DOC)

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Formal analysis: WS CT KW RjZ.

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Supervision: SbZ.

Validation: WS CT RjZ.

Visualization: WS CT SbZ.

Writing – original draft: WS CT SbZ.

Writing – review & editing: WS CT KW SbZ.

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