

Systematic Review

Relationship between Prediction of Platelet-Lymphocyte Ratio and Atrial Fibrillation in Perioperative Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: The platelet-to-lymphocyte ratio (PLR) could be a convenient method to predict atrial fibrillation (AF) likelihood and, in turn, to determine the patients' postoperative trajectory. This study aimed to evaluate the prognostic effect of pre-intervention PLR in predicting the occurrence of AF after surgery. **Methods:** PubMed, Embase, and the Cochrane library were searched for available papers published up to October 2023. The primary outcome was the odds ratio (OR) of numerical PLR in the model predicting AF occurrence. The random-effects model was used in all analyses. **Results:** Six studies were included. There were 1197 patients with AF and 1998 patients without AF. The combined analysis of all six studies showed that PLR was associated with AF after surgery (OR = 1.01, 95% confidence interval (CI): 1.00–1.01, $p = 0.000$; $I^2 = 43.4%$, $p_{\text{heterogeneity}} = 0.116$). Three studies examined PLR before coronary artery bypass graft (CABG), and the meta-analysis showed that PLR was associated with AF after CABG (OR = 1.01, 95% CI: 1.00–1.02, $p = 0.002$; $I^2 = 0.0%$, $p_{\text{heterogeneity}} = 0.894$). The sensitivity analysis showed that the results were not robust. There was no obvious publication bias. **Conclusions:** Pre-intervention PLR was significantly associated with post-intervention AF in patients who underwent CABG or other surgeries. Elevated PLR is a risk factor for postoperative atrial fibrillation.

Keywords

atrial fibrillation; platelet-to-lymphocyte ratio; post-intervention; meta-analysis

Introduction

Atrial fibrillation (AF) is a common supraventricular tachyarrhythmia caused by uncoordinated atrial activation and associated with an irregularly irregular ventricular response [1,2]. AF can range from asymptomatic to presenting a variety of symptoms, including dizziness, shortness of breath, palpitations, fatigue, and chest pain [3]. In developed countries, the AF prevalence in the general population is approximately 1%–2% (this accounts for almost 10% of adults over 80 years of age) [4–6]. Patients with AF often exhibit an elevated risk of thromboembolism, which in particular, can lead to stroke [4–6]. AF has a significant impact on patients' quality of life, making it a major determinant [4–6]. The underlying causes of AF are broad and can include endocrine diseases, structural heart disease, coronary artery disease (CAD), metabolic disorders, hypertension, and the use of certain medications [2,5]. In chest and heart surgery, atrial fibrillation is the most common postoperative complication. In terms of surgical causes, there are several factors that can contribute to an increase in post-operative complications. Factors that can contribute to surgical complications include the type of procedure performed, excessive bleeding during the operation, electrolyte imbalances, low blood pressure, elevated inflammatory markers, and oxygen deprivation [7,8]. Postoperative atrial fibrillation (POAF) is a health condition that can lead to an increase in various adverse outcomes, including morbidity, mortality, extended hospital stay, and an elevated thromboembolic risk [9].

Coronary artery bypass graft (CABG) is one of the two main surgical options for revascularization after acute myocardial infarction [10], besides percutaneous coronary intervention [11]. CABG is a major surgery that involves harvesting venous or arterial conduits and using them to bypass the atheromatous blockages in coronary arteries and allow reperfusion of the ischemic myocardium [10]. AF is

the most prevalent type of post-CABG rhythm disorder observed in approximately 20%–50% of patients undergoing this procedure [12–15]. After cardiac surgery, the development of AF is linked to increased morbidity, mortality, longer hospital stays, and a two to three-fold increase in postoperative stroke [12–14]. AF cannot be cured, pharmacological strategies used in the medical management of AF are aimed at reducing episodes. Some common strategies include using dofetilide to manage heart rate and rhythm [1,6]. It is crucial to identify potential risk factors for atrial fibrillation, as this will allow for the implementation of necessary preventive measures.

Inflammation and oxidative stress are known to significantly contribute to the development of AF in patients following both cardiac and noncardiac surgeries [16]. Especially inflammation, which is the main underlying contributor to several cardiovascular diseases, AF is frequently associated with co-occurring conditions such as hypertension, coronary artery disease (CAD), and heart failure [2]. Platelets are associated with both thrombosis and inflammation and play an important role in the pathogenesis of AF [17]. Circulating platelets secrete many crucial mediators of coagulation, inflammation, thrombosis, and atherosclerosis [18]. Emerging inflammatory biomarkers, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), for example, have been studied extensively in recent years across multiple surgical disciplines [19]. The PLR is a unique, low-cost, and easily accessible indicator of inflammation and mortality [20,21], especially in patients with cardiovascular diseases [22–24]. Preoperative PLR is associated with the occurrence of major cardiovascular adverse events after surgery in patients with CAD [25]. Since the development of AF involves inflammation and shares many risk factors with other cardiovascular diseases, it has been suggested that the PLR could be used to predict AF [26–29]. They proposed that the preoperative PLR could be a convenient method to predict AF likelihood and, in turn, to determine the patients' postoperative trajectory. Still, the association between the preoperative PLR and the development of post-CABG AF is controversial, with studies reporting associations [26,27,30] and others reporting no associations [28,29]. Of note, the value of post-CABG PLR is still inconclusive because of the deep changes in immune cells, inflammation, and platelets caused by surgical trauma [31], making the preoperative PLR more meaningful for prognosis. Therefore, we conducted this meta-analysis to evaluate the relationship between preoperative PLR and postoperative atrial fibrillation.

Materials and Methods

Literature Search

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32]. PubMed, Embase, and the Cochrane library were searched for available papers published up to October 2023, followed by screening based on following criteria: (1) Patients undergoing chest or heart surgery; (2) Outcomes: PLR; (3) Exposure: any type of AF; (4) Study designs including case-control studies, cross-sectional studies, and retrospective/prospective cohort studies. Studies with the following exclusion criteria were not included in our research: (1) Studies without surgical intervention; (2) Studies with odds ratio (OR) value of PLR cannot be obtained with incomplete data; (3) Case reports. The key words used for searching included 'Atrial Fibrillation' and 'platelet lymphocyte'. Duplicated studies were identified when multiple studies reported on the same patient population, and only the most proper and qualifiable research was selected for analysis. The detailed search strategy could be found in **Supplementary Table 1**.

Data Extraction

Duplicates were first removed automatically using EndNote X9 (The EndNote Team, Clarivate, Philadelphia, PA, USA), then two independent authors (LY and YaH) examined the titles and abstracts of all retained studies from the previous step to evaluate their eligibility. Finally, the full texts of all studies that may have met the eligibility criteria were downloaded from the database after being bypassed the title and abstract screening process. To resolve discrepancies between the authors, the consensus principle was employed.

Study characteristics (authors, country, year of publication, sample size, study design, sex, and age of patients, type of analysis), parameters (characteristics of the patients and the definition of AF), and the primary outcome (the OR of numerical PLR in the model predicting the occurrence of AF) were extracted and reviewed by two different investigators (LY and YaH) according to a pre-specified protocol. Discrepancies were resolved by discussion until a consensus was reached.

Data Synthesis

ORs and confidence intervals (CIs) that indicated the prognostic effect of PLR in univariable or multivariable regression models were extracted. Among them, three studies used univariate analysis and other three studies used multivariate conditional logistic regression model (Table 1, Ref. [26–30,33]).

Table 1. Literature search and study characteristic.

Author, year	Country	Study type	Population	Diagnosis of AF	Sample size		Male, %		Age, year		Type of analysis
					AF	Non-AF	AF	Non-AF	AF	Non-AF	
Dereli, 2019 [26]	Turkey	Prospective cohort study	Restoration to sinus rhythm from non-valvular AF	AF episode lasting for at least 5 min in the 12-lead ECGs	108	168	44.4	52.4	65.0 ± 9.4	57.4 ± 12.0	Univariate analysis
Aksoy, 2020 [30]	Turkey	Case-control	Underwent CABG	Paroxysmal AF episode lasting more than 30 s in the 12-lead ECGs	136	279	70.9	67.7	67.5 ± 8.9	60.5 ± 12.4	Univariate analysis
Gungor, 2017 [27]	Turkey	Case-control	Underwent CABG	Irregular arrhythmia lasting for at least 5 min before hospital discharge	50	75	76	77	67.0 ± 9.5	61.1 ± 9.1	Univariate analysis
Navani, 2020 [28]	Australia	Case-control	Underwent CABG	Evidence of new AF detected by ECG or continuous monitoring throughout the postoperative period that required treatment	495	962	84	81	69 (63–74)	64 (56–71)	Multivariate analysis
Zhang, 2018 [29]	China	Case-control	Non-valvular AF/control	ACC/AHA/ESC 2001 Guidelines	375	375	53.7	53.7	57.33 ± 12.19	57.33 ± 12.19	Multivariate analysis
Sivri, 2022 [33]	Turkey	Retrospective cohort study	underwent standard thoracotomy and the video-associated thoracic surgery	The absence of P waves on standard 12-lead ECGs	32	138	87.5	90.6	71.28 ± 7.27	64.69 ± 10.31	Multivariate analysis

AF, atrial fibrillation; POAF, postoperative atrial fibrillation; CABG, coronary artery bypass graft; ECG, electrocardiography; ACC, American College of Cardiology; ACHD, adult congenital heart disease; AHA, American Heart Association; ESC, European Society of Cardiology.

In multivariate conditional logistic regression model, the adjusted ORs with the greatest number of covariables in the model were used for analysis. If the adjusted OR was not reported in the study, the unadjusted OR in the univariable model was used as an alternative.

Quality of the Evidence

Ultimately, one prospective cohort study and five case-control studies entered the analysis. The level of evidence was assessed in conformity with the Cochrane Handbook [34] and the Newcastle-Ottawa Scale (NOS) [35] criteria for cohort study and case-control study, respectively. The quality assessments were conducted independently by two professional authors (LY and YaH) (Supplementary Table 2). Discrepancies in the assessment were resolved through discussion until a consensus was reached.

Statistical Analysis

All analyses were performed using STATA SE 14.0 (Stata Corp, College Station, TX, USA). Effects and corresponding 95% CIs were used to compare the outcomes. Statistical heterogeneity among studies was calculated using Cochran's Q-test and the I^2 index. I^2 : 0%–25% indicates no heterogeneity; 25%–50%, modest heterogeneity; 50%, high heterogeneity. The random-effects model was used whether statistical heterogeneity was presented or not since the sample size was variable among studies, which would potentially increase the heterogeneity in statistics and lead to a biased assessment. We carried out a thorough sensitivity analysis to ensure the reliability of our findings and to scrutinize the impact of each individual study by sequentially excluding one from the analysis. Publication bias was assessed via funnel plot and Egger's test, albeit only six studies were included in this analysis, in which case the conclusion must be taken with caution [34,36]. p -values < 0.05 were considered statistically different.

Results

Selection and Characteristics of the Studies

Fig. 1 presents the study selection process. The initial search yielded 279 records; 17 duplicates were excluded. Then, 262 records were screened, and 239 were excluded. Twenty-three full-text articles and abstracts were assessed for eligibility, and 17 were excluded (population, $n = 9$, outcomes, $n = 3$; intervention, $n = 5$).

Finally, six studies were included (Table 1). Four studies were from Turkey [26,27,30,33], one from Australia [28], and one from China [29]. There were 1197 patients with AF and 1998 patients without AF. One study [29] scored 9 stars on the NOS, and the remaining five studies [26–28,30,33] scored 8 stars.

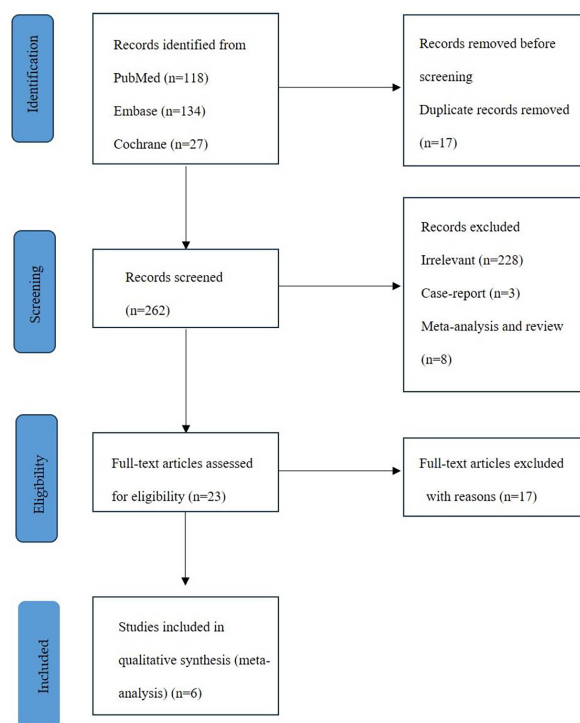


Fig. 1. Flow chart.

PLR is Associated with AF after Surgery

The combined analysis of all six studies [26–30,33] showed that PLR was associated with AF after surgery (OR = 1.01, 95% CI: 1.00–1.01, $p = 0.000$; $I^2 = 43.4%$, $p_{\text{heterogeneity}} = 0.116$) (Fig. 2A), with modest heterogeneity.

PLR is Associated with AF after CABG

Three studies examined PLR after CABG [27,28,30]. The meta-analysis showed that PLR was associated with AF after CABG (OR = 1.01, 95% CI: 1.00–1.02, $p = 0.002$; $I^2 = 0.0%$, $p_{\text{heterogeneity}} = 0.894$) (Fig. 2B). There was no heterogeneity observed.

Sensitivity Analysis

We carried out a thorough sensitivity analysis to ensure the reliability of our findings and to scrutinize the impact of each individual study by sequentially excluding one from the analysis. The sensitivity analysis showed that Sivri's study [33] had a great influence on the results of the association between PLR and post-intervention AF (Fig. 2C).

Publication Bias

Although the results must be taken with caution because the number of studies was <10 [34,36], the fun-

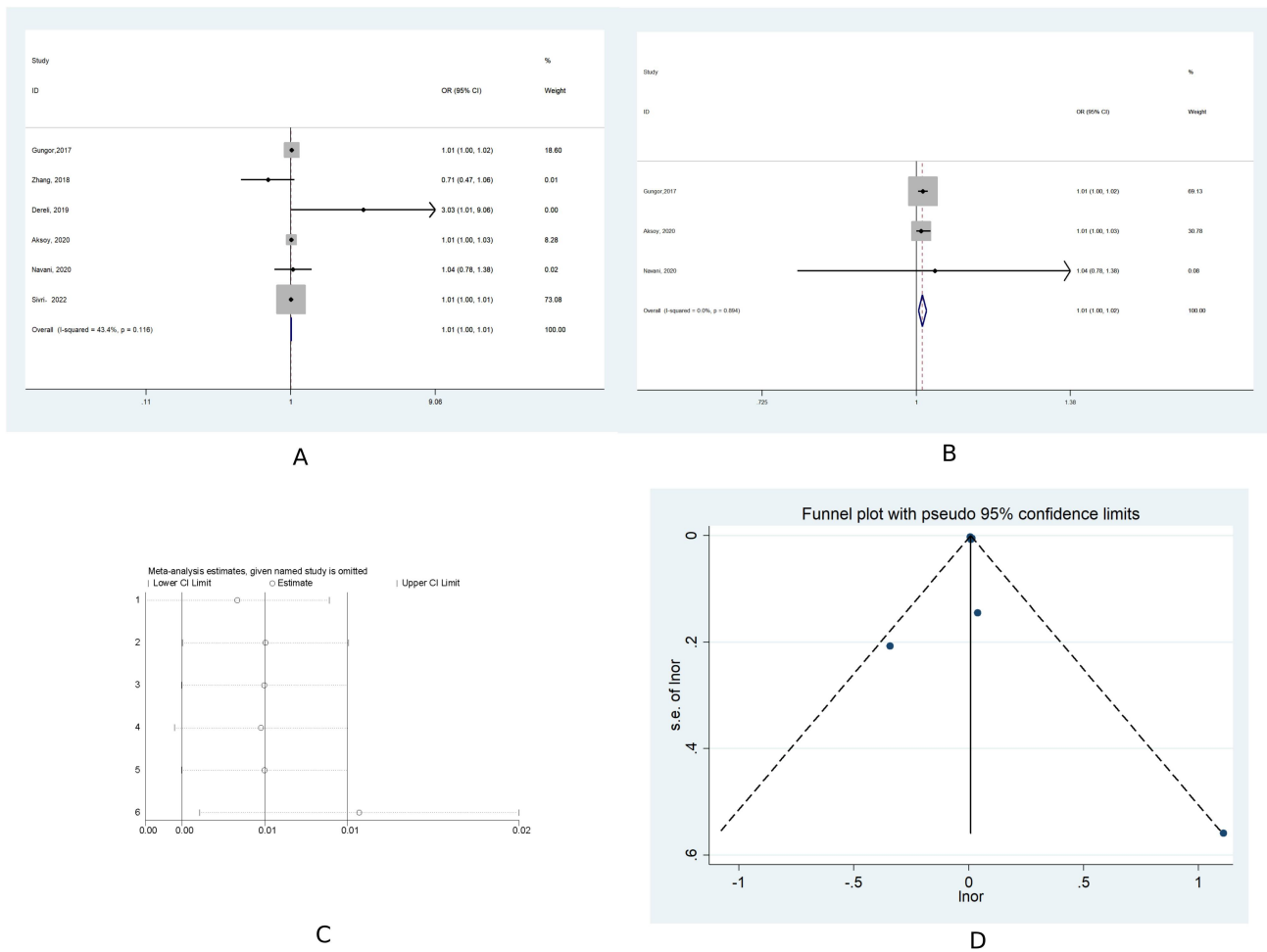


Fig. 2. Correlation between PLR and AF. (A) Forest plot for AF in all studies. (B) Forest plot of the association between pre-intervention platelet-to-lymphocyte ratio (PLR) and post-intervention AF in patients who underwent CABG. (C) Sensitivity analysis. (D) Funnel plot of log odds ratio to explore publication bias.

nel plot suggests that there is no obvious publication bias (Fig. 2D), which was further proved using Egger's test ($p = 0.652$).

Discussion

The goal of this meta-analysis was to examine the predictive power of pre-operative PLR for predicting AF after surgery. The results showed that PLR was associated with post-intervention AF, and pre-intervention PLR was also significantly associated with post-intervention AF in patients who underwent CABG.

Since surgery implies trauma and inflammation and that inflammation participates in the onset of AF [37], the occurrence of AF is common after surgery, at 4%–60% for all surgeries, 0.3%–29% for non-cardio-thoracic surgery, 12%–19% for abdominal surgery, and 4.8% for arthroplasty [38]. Therefore, inflammatory markers could be convenient tools for evaluating the risk of AF after surgery. A vari-

ety of inflammatory markers has been explored for association with AF, including C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor (TNF)- α , white blood cell (WBC) count, CD14⁺CD16⁺ monocytes, red blood cell distribution width (RDW), myeloperoxidase (MPO), galectin-3, and fibrinogen, but these biomarkers yield inconsistent results or display low sensitivity/specificity for AF [37,39]. Previous research has indicated that PLR offers a more comprehensive understanding of hemostasis and inflammatory pathways than platelet count alone. The model has proven effective in predicting outcomes associated with various malignancies, ST-elevation myocardial infarction, and chronic inflammatory diseases [40,41]. The PLR has recently been shown to be associated with the occurrence and recurrence of AF and with a better predictive value than other markers [42,43]. The PLR can predict the occurrence of AF [44]. However, as mentioned earlier, the association between the preoperative PLR and the development of post-CABG AF is controversial. In the present meta-analysis, our results indicated that pre-intervention

PLR was associated with post-intervention AF when considering all surgery types. Which is consistent with previous studies that PLR is a risk factor for atrial fibrillation. There was modest heterogeneity observed. Sensitivity analysis showed that Sivri's [33] study had a great influence on the stability of the analysis. One possible reason may be that advanced age was identified as a primary risk factor for AF. This particular study focused on participants aged over 60. Therefore, more research is needed for further verification in the future.

In patients with CABG, the OR was 1.01, $p = 0.002$, which indicated that PLR was associated with AF after CABG, further supported that PLR was a risk factor for postoperative atrial fibrillation. There was no heterogeneity observed. CAD itself is a risk factor for AF [2,5,45], and the combination of CAD and surgery could increase the risk of post-intervention AF. CABG is a complex procedure that involves significant trauma and inflammation [12], and AF after CABG occurs in approximately 15%–30% of patients [12,13]. In this meta-analysis, the PLR was associated with post-intervention AF in patients who underwent CABG. Platelets are the source of inflammatory mediators and lymphocytes have been shown to regulate the immune response during all progressive stages of atherosclerosis [46]. The number of lymphocytes is expected to decrease due to lymphocyte apoptosis in cases associated with increased inflammation [47]. In this context, the results of our study are also compatible with this pathogenesis of the inflammatory process. Our results supported that elevated PLR is a risk factor for postoperative atrial fibrillation, and PLR can be used as a predictor of postoperative atrial fibrillation. Still, only three studies were included, more research is needed for further verification the future.

The PLR is a readily available marker. It simply involves dividing the values of two blood cells that are routinely measured in all patients admitted for major surgery in almost all hospitals [44]. Calculating the PLR does not require complicated calculations or specific tools/software [44]. Since it allows a rapid and inexpensive assessment of prognosis in several conditions, it is probably a cost-effective marker, although no studies have specifically evaluated that aspect yet. Future studies and meta-analyses should compare PLR with other inflammatory markers to determine which markers could be stronger than others. This meta-analysis has limitations that must be considered against its conclusions. First, the number of patients was small. In addition, five studies were retrospective, which might undermine the combined results due to the biases inherited from all studies. Second, because there is no universally accepted cutoff positivity threshold for PLR, we excluded studies that treated PLR as a categorical variable. Thirdly, discrepancies exist in the reporting of patient baseline characteristics across the various studies. Meta-regression analysis of important predefined covariables was not possible, and the influence of age, body mass index,

comorbidities (hypertension, diabetes, and obesity), sex, smoking, and alcohol, for example, could not be determined. Still, the ORs from multivariable analyses were extracted from the studies when available, and the influence of these variables on the extracted ORs should have been ruled out. Finally, our sensitivity analysis revealed that the study's results were not stable or robust enough. Furthermore, although publication bias was assessed, the number of studies included was <10 , in which case the funnel plots and test could yield misleading results [34,36].

Conclusions

In conclusion, pre-intervention PLR was significantly associated with post-intervention AF in patients who underwent chest and heart surgery. Elevated PLR is a risk factor for postoperative atrial fibrillation, and PLR can be used as a predictor of postoperative atrial fibrillation. Further explorations of the difference between baseline PLR and post-intervention. To determine if the predictive value of the different PLR measurements is independent of other factors, both AF and a combined multivariable analysis of the PLR values with other hematological inflammatory biomarkers are required.

Abbreviations

PLR, platelet-to-lymphocyte ratio; AF, atrial fibrillation; OR, odds ratio; CABG, coronary artery bypass graft; CAD, coronary artery disease; NLR, neutrophil-to-lymphocyte ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CIs, confidence intervals; NOS, Newcastle-Ottawa Scale; CRP, C-reactive protein; TNF, tumor necrosis factor; WBC, white blood cell; RDW, red blood cell distribution width; MPO, myeloperoxidase.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Author Contributions

BilinY and JG conceived and supervised the study; BiliY and BilinY analysed data; YoH and YaH participated in acquisition, analysis, or interpretation of data and draft the manuscript; LY and BilinY made manuscript revisions. All authors reviewed the results and approved the final version of the manuscript. All authors contributed to editorial

changes in the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.59958/hsf.6851>.

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