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Prediction of Paroxysmal Atrial Fibrillation in Patients with Sinus Rhythm

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Abstract

Objective: To create a tool for the prediction of paroxysmal atrial fibrillation (PAF) in patients with sinus rhythm.

Methods: Single-center, case-control study. None of the patients had a prior diagnosis of AF or reported symptoms of heart arrhythmias. Among the cohort of 6,630 individuals, paroxysms of AF were incidentally detected during 24-hours Holter ECG monitoring in 97 patients (main group). The control group - 99 patients from the same primary cohort without PAF. We assessed supraventricular and ventricular ectopic activity, the presence of pauses and blocks, changes of ST segment, QT interval durations, and heart rate variability.

Results: We formulated a regression equation to estimate the probability of PAF in patients with sinus rhythm. The most significant risk predictors: early "P on T" premature ectopic complexes ($p<0.0001$); coupled premature ventricular ectopic complexes ($p=0.021$); ventricular allorhythmias (OR=0.997). Other analyzed factors, including the frequency of both atrial and atrioventricular premature ectopic complexes, as well as single ventricular ectopic complexes, did not exhibit a statistically significant effect on the risk of PAF, according to this model.

Conclusion: The final regression equation, based on the evaluation of data from 24-hours Holter ECG monitoring, incorporates the following criteria: gender, the number of atrial and atrioventricular supraventricular complexes, the count of single and paired ventricular complexes, variations in rhythms with ventricular complexes, as well as the presence or absence of early "P on T" complexes (AUC=0.996).

Keywords: atrial fibrillation, premature complexes, paroxysmal atrial fibrillation, predictive equation.

Introduction

Paroxysmal atrial fibrillation (PAF) is one of the most common heart arrhythmia all over the world, characterized by intermittent episodes of atrial fibrillation (AF) that typically resolve spontaneously. It poses significant clinical challenges due to its potential to progress to persistent forms of AF, leading to increased morbidity and mortality. Understanding the risk factors and physiological mechanisms underlying PAF is crucial for early identification and intervention in at-risk populations.

Recent studies have highlighted the importance of identifying patients with sinus rhythm who have higher risk of developing PAF. This is particularly relevant for asymptomatic patients who have PAF episodes and due to the limitations of current diagnostic methods. Advances in technology and analytical methodologies have opened new avenues for risk stratification, including the use of machine learning algorithms and wearable devices that can monitor cardiac rhythm continuously [1–4].

Risk factors, associated with PAF, include age, arterial hypertension, diabetes mellitus, obesity, and structural heart disease, but emerging evidence suggests that biomarkers and genetic predisposition may also play significant roles [5–8]. Additionally, lifestyle factors, such as alcohol consumption and physical inactivity, have been implicated in the development of PAF, indicating that preventive strategies could be implemented in appropriate patient populations [9–12].

The integration of these diverse risk factors into predictive models holds promise for stratifying patients with sinus rhythm, allowing for more personalized approaches to the management and prevention of PAF. Recent research efforts have focused on developing and validating such predictive models, which may incorporate clinical parameters, echocardiographic findings, and novel biomarkers [13, 14]. As the field of cardiology moves towards a more precision-based approach, understanding how to effectively predict PAF in patients with sinus rhythm may provide critical insights for clinicians and patients alike.

When improving the possibility of PAF prediction before its manifestation, prevention strategies take a leading role, including lifestyle modification, pharmacological therapy, or even catheter ablation in select populations, which could significantly improve patients outcomes while reducing healthcare costs related to PAF complications [15–18].

Objective: To create a tool for the prediction of PAF in patients with sinus rhythm.

Methods

A single-center, case-control study was conducted. We analyzed the data from 6,630 patients who underwent routine examinations of 24-hours Holter ECG monitoring during hospitalization in Samara State Medical University Clinics. None of the patients had a prior diagnosis of AF or reported symptoms, related to rhythm disturbances before the study commenced. Among this cohort of 6,630 individuals, paroxysms of AF were incidentally detected during 24-hours Holter ECG monitoring in 97 patients. They were included into the main group. The control group consisted of 99 patients from the same primary cohort, without paroxysms of AF. We selected the patients for the control group from the whole cohort the way that both groups were equal in terms of anthropometric parameters and comorbidities.

All patients underwent standard laboratory and instrumental examinations. In addition to the 24-hours Holter ECG monitoring, instrumental methods included transthoracic echocardiography and Doppler ultrasound of the brachiocephalic arteries. Stress echocardiography with physical exercise or pharmacological testing, as well as coronary angiography, were performed if indicated. During the data analysis of 24-hours Holter ECG monitoring, we studied the following key parameters: ECG registration time, heart rhythm pacemaker, supraventricular and ventricular ectopic activity, the presence of pauses and blocks, changes of the ST segment, QT interval durations, and heart rate variability. Special attention was given to the presence of early extrasystoles of the “P on T” and “R on T” types.

The research was conducted in accordance with the Helsinki Declaration, and the local ethical committee approved study protocol (№248 dated 27.04.2022, SamSMU University Ethical committee). All patients signed an informed agreement to participate in the study.

In statistical analysis, we followed the principles of evidence-based medicine. Initially, the normality of the distribution of the analyzed parameters was determined. For normally distributed data, parametric criteria were used (quantitative variables were characterized by calculating the mean and standard deviation; intergroup comparisons were performed using one-way ANOVA with F-statistic, degrees of freedom “df,” and statistical significance “p”). For non-normally distributed data, non-parametric criteria were applied (for quantitative indicators, medians and the first and third quartiles – Q1 and Q3 – were provided; intergroup comparisons were conducted using the Kruskal-Wallis method, indicating values for H and “p”). Differences between groups were considered statistically significant at $p \leq 0.05$. For all statistical tests, the criterion for statistical significance was set at $p \leq 0.05$. Statistical analysis was performed using MedCalc® Statistical Software version 20.118 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022), GraphPad Prism for Windows, version 10.1.0 (GraphPad Software, San Diego, California, USA, www.graphpad.com), and the open-source R software environment (https://cran.rstudio.com/).

Results

The main and control groups had no statistically significant differences in anthropometric parameters or comorbidities. However, the analysis of data from 24-hours Holter ECG monitoring revealed statistically significant variations in both supraventricular and ventricular ectopic activity characteristics (see Table 1 on the next page).

In summary, the parameters observed in 24-hours Holter ECG monitoring, such as the presence of ectopic complexes and paroxysmal tachycardia, occurred significantly more frequently and with higher values in the main group with PAF. Specifically, the vast majority (97.9%) of patients in the main group with diagnosed PAF exhibited early atrial ectopic complexes of the “P on T” type, compared to only 4.0% in the control group (odds ratio [OR] = 8461.648 [382.1983; 187336]). The frequency of supraventricular ectopic complexes was also significantly higher in the main group, including single, coupled, and grouped ectopic complexes. Additionally, the interval durations were notably longer in the group with PAF. However, the rates of ventricular ectopic complexes and ST segment depression did not differ significantly between the groups. In other words, patients of the main group with PAF demonstrated distinctive rhythm and conduction changes when compared to the control group, despite both groups being equal in key anthropometric characteristics and comorbidities.

To develop a predictive tool for PAF in patients with sinus rhythm, we analyzed the relevance and significance of various parameters, including early "P on T" ectopic complexes, coupled ventricular ectopic complexes, and ventricular allorhythmias. The presence of early “P on T” premature ectopic complexes substantially increased the likelihood of developing PAF by a factor of 8461 compared to its absence ($p<0.0001$). Conversely, an increase in paired premature ventricular ectopic complexes

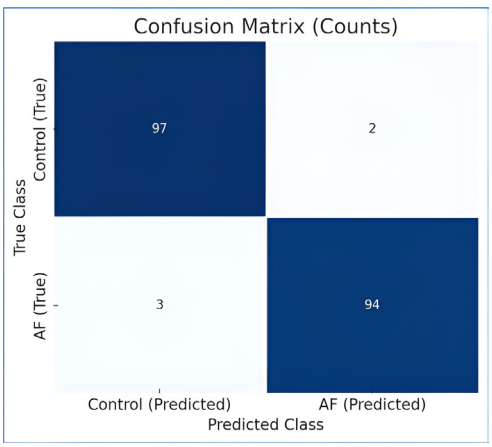

Figure 1 – Confusion plot. AF – main group (n=97), control – control group (n=99)

Table 1 24-hours Holter ECG monitoring data within the main and control groups

Parameters, Median (Q1, Q3)	Main group n=97	Control group n=99	Statistics
Gender, n (%)			
F	53 (27.04)	53 (27.04)	χ2=0.000, p=0.991
M	44 (22.45)	46 (23.47)	
Age, years old	72.0 (65.0, 78.0)	71.0 (64.0, 79.0)	H=0.007, p=0.933
ECG time registration, hours	22.7 (21.9, 23.2)	22.3 (21.4, 23.1)	H=1.376, p=0.120
Time of recorded AF, seconds	81.0 (14.0, 8925.0)	0.0 (0.0, 0.0)	H=167.876, p<0.001
Heart rate in AF	107.0 (94.0, 117.0)	Not applicable	H=167.142, p<0.001
Supraventricular paroxysmal tachycardia, seconds	5.0 (0.0, 34.0)	0.0 (0.0, 9.0)	H=9.840, p=0.002
Ventricular paroxysmal tachycardia, seconds	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	H=0.099, p=0.753
Supraventricular extrasystoles	633.0 (284.0, 2098.0)	79.0 (27.5, 349.5)	H=40.635, p<0.001
Single supraventricular extrasystoles	461.0 (238.0, 1767.0)	69.0 (22.5, 315.0)	H=37.952, p<0.001
Coupled and group supraventricular extrasystoles	26.0 (6.0, 93.0)	4.0 (1.0, 12.0)	H=38.272, p<0.001
Allorhythmia in supraventricular extrasystoles	24.0 (1.0, 401.0)	0.0 (0.0, 9.5)	H=31.647, p<0.001
Atrial extrasystoles	602.0 (262.0, 2028.0)	74.0 (27.5, 314.0)	H=36.843, p<0.001
Ventricular extrasystoles	24.0 (3.0, 149.0)	16.0 (3.0, 488.5)	H=0.176, p=0.675
Single ventricular extrasystoles	20.0 (2.0, 143.0)	14.0 (2.0, 328.5)	H=0.121, p=0.727
Coupled ventricular extrasystoles	0.0 (0.0, 6.0)	0.0 (0.0, 2.0)	H=2.100, p=0.147
Allorhythmia in ventricular extrasystoles	0.0 (0.0, 0.0)	0.0 (0.0, 3.0)	H=0.193, p=0.661
Extrasystoles type «R on T»	2.0 (1.0, 5.0)	0.0 (0.0, 0.0)	H=74.763, p<0.001
Extrasystoles type «P on T», n (%)	95 (97.9%)	4 (4.0%)	χ2= 172.81, p<0.001
QT interval max, seconds	0.5 (0.5, 0.6)	0.5 (0.5, 0.6)	H=2.495, p=0.114
RR interval max, seconds	1.7 (1.6, 1.9)	1.5 (1.4, 1.8)	H=14.172, p<0.001
Loss of QRS complex	0.0 (0.0, 2.0)	0.0 (0.0, 0.0)	H=11.732, p=0.001
ST depression, n (%)	13 (6.63%)	8 (4.08%)	χ2=2.377, p=0.305
Pacemaker, n (%)	2 (1.02%)	0 (0%)	χ2=0.526, p=0.468

AF – atrial fibrillation; ECG – electrocardiography; F – feminine; M – masculine.

reduced the probability of PAF, with this effect also being statistically significant (p=0.021). Moreover, a greater number of episodes of ventricular allorhythmia was associated with a lower risk of PAF (OR=0.997) (see Figure 1).

Based on these findings, we formulated a regression equation to estimate the probability of PAF in patients with sinus rhythm. We identified the following as the most significant risk predictors for developing PAF:

1) The presence of early "P on T" premature ectopic complexes, which had a highly significant impact (p<0.0001). When "P on T" ectopic complexes were present, the likelihood of developing PAF increased 8461 times compared to their absence, highlighting the strong predictive value of this factor.

2) Coupled premature ventricular ectopic complexes, where an increase in their number correlated with a reduced probability of PAF, also with statistical significance (p=0.021).

3) Ventricular allorhythmias. A higher incidence of these episodes during ventricular ectopic activity was linked to a diminished risk of PAF (OR=0.997).

Other analyzed factors, including the frequency of both atrial and atrioventricular premature ectopic complexes, as well as single ventricular ectopic complexes, did not exhibit a statistically significant effect on the risk of PAF, according to this model.

The proposed assessment model demonstrated a high accuracy in forecasting. We validated our proposed model on the same cohort of the analyzed patients due to the principles of evidence-based statistical analysis. The ROC curve analysis revealed that the area under the curve (AUC) was 0.996, with an optimal risk coefficient for predicting PAF set at 0.5, resulting in a prediction accuracy of 97.45%. We named the developed equation "Arfa" (see Figure 2).

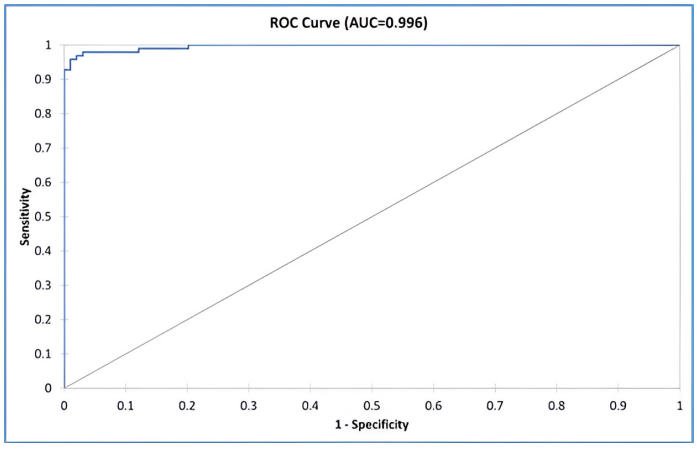

Figure 2 – ROC-curve of "Arfa" (AUC=0,996)

The final regression equation, based on the evaluation of data from 24-hours Holter ECG monitoring, incorporates the following criteria: gender, the number of atrial and atrioventricular supraventricular complexes, the count of single and paired ventricular complexes, variations in rhythms with ventricular complexes, as well as the presence or absence of early "P on T" extrasystoles. This predictive tool for the onset of PAF in patients with sinus rhythm, utilizing the "Arfa" equation, recommends the implementation of the following regression equation:

Table 2 Model parameters (groups of variables)

Parameter	Importance	Standard error	Wald Chi-Square	Pr>Chi²	Wald Lower bound (95%)	Wald Upper bound (95%)	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound (95%)
Atrial extrasystoles	0.001	0.000	3.966	0.046	0.000	0.001	1.000677172	1.000010727	1.001344061
Ventricular extrasystoles	-0.001	0.003	0.070	0.791	-0.007	0.005	0.9991973805	0.9932764343	1.005153622
Single ventricular extrasystoles	-0.002	0.002	0.652	0.419	-0.006	0.003	0.9981502839	0.9936747847	1.002645941
Coupled ventricular extrasystoles	0.017	0.015	1.211	0.271	-0.013	0.046	1.016670605	0.9871675159	1.047055442
Ventricular allorhythmias	-0.006	0.005	1.477	0.224	-0.016	0.004	0.9940329032	0.9844853485	1.00367305
Gender - M	-2.040	3.226	0.400	0.527	-8.362	4.283	0.1300607651	0.0002334862027	72.44883181
«P on T» extrasystoles	17.475	11.945	2.140	0.143	-5.936	40.887	38857742.95	0.002642938799	5.71305E+17

M – masculine.

Table 3 Standard coefficients (Variable group)

Parameter	Importance	Standard error	Wald Chi-Square	Pr>Chi²	Wald Lower bound (95%)	Wald Upper bound (95%)	PL Lower bound (95%)	PL Upper bound (95%)
Atrial extrasystoles	1.406	0.706	3.966	0.046	0.022	2.789	0	0
Ventricular extrasystoles	-0.648	2.446	0.070	0.791	-5.443	4.147	0	0
Single ventricular extrasystoles	-0.982	1.216	0.652	0.419	-3.366	1.402	0	0
Coupled ventricular extrasystoles	1.654	1.503	1.211	0.271	-1.292	4.601	0	0
Ventricular allorhythmias	-1.706	1.404	1.477	0.224	-4.458	1.045	0	0
Gender - M	-0.559	0.884	0.400	0.527	-2.291	1.173	0	0
«P on T» extrasystoles	4.817	3.292	2.140	0.143	-1.636	11.270	0	0

M – masculine.

Figure 3 – Standard coefficients (95% confidential interval)

P on T – extrasystoles type "P on T"; Paried VE – paired premature ventricular contractions; Single VE - single premature ventricular contractions; AV Ectopics – supraventricular extrasystoles; Atrial Ectopics – atrial extrasystoles.

Pr (Arfa) = 1 / (1 + EXP (- (- 3,65982 + 0,000144 * Atrial ES + 0,000354 * Atrioventricular ES + 0,000842 * Single ventricular ES - 0,01613 * Couple ventricular ES - 0,002863 * Ventricular allorhythmias - 1,596521 * Gender m + 9,043299 * "P on T" ES))).

Notes: ES – premature complexes, gender f = 0, m = 1; "P on T" ES = 1, absence of «P on T» ES = 0.

Hosmer-Lemeshow test:

Pr (Arfa) = 1 / (1 + EXP (- (- 4.428948 + 0.000677 * Atrial ES - 0.000803 * Atrioventricular ES - 0.001851 * Single ventricular ES + 0.016533 * Couple ventricular ES - 0.005985 * Ventricular allorhythmias - 2.039754 * Gender m + 17.475418 * "P on T" ES -1))).

Notes. ES – premature complexes.

The model parameters are detailed in Tables 2 and 3, as well as in Figure 3.

The risk of developing PAF in patients with sinus rhythm can be assessed using the "Arfa" regression equation as follows:

If Pr (Arfa) > 0.5, there is a high risk of PAF, in which case we recommend treating ectopic complexes and subsequently

monitoring with a 24-hour Holter ECG. Conversely, if Pr (Arfa) < 0.5, the risk of developing PAF is considered low.

Discussion

PAF remains a significant clinical challenge, given its association with increased morbidity and mortality. The development of predictive models for PAF in patients maintaining sinus rhythm plays crucial role for identifying the individuals at heightened risk who may benefit from preventive strategies. Earlier investigations demonstrated the utility of various clinical, demographic, and electrophysiological factors in predicting PAF recurrence [19, 20]. Moreover, the incorporation of machine learning algorithms appears promising, providing enhanced predictive power over traditional models [21].

Recent literature emphasizes the role of clinical risk factors such as arterial hypertension, heart failure, and age as key contributors to the development of PAF [5, 8]. In the publications, it was demonstrated that advancing age is a significant predictor, with a clear relationship between age and the likelihood of developing PAF observed. Older adults exhibited a higher burden of AF due to the structural and electrical remodeling in the heart [11, 12].

Furthermore, comorbidities, such as obesity and diabetes mellitus significantly enhance the risk of PAF, reinforcing insights from several recent studies. Obesity, in particular, affects atrial structure through increased stretch and pressure, thereby facilitating the onset of arrhythmias [22, 23].

Another noteworthy aspect of our predictive modeling involves the integration of sleep apnea as a potential risk factor for PAF [24]. Nocturnal hypoxia and sympathetic overactivity stemming from obstructive sleep apnea may lead to atrial remodeling and increased arrhythmogenicity. Although this study did not focus solely on obstructive sleep apnea, the patterns suggest that screening patients for sleep-disordered breathing could be a vital component of the risk stratification strategy in those with AF.

Lifestyle factors also surfaced as significant predictors of PAF. So, smoking and alcohol consumption have been implicated in the development of PAF. Recent studies suggest that modifiable lifestyle can significantly reduce the risk of AF developing [9, 11, 12]. The advent of wearable technology and digital health has revolutionized how we monitor patients with potential arrhythmias. Continuous heart rhythm monitoring facilitates plays an important role in early detection of PAF episodes and offers the potential benefit for personalized strategies [13, 18].

Despite above-mentioned advances, there remain limitations and contradictions. There is still no universal model for predicting the development of AF that could be used in the everyday clinical practice.

The routine method of 24-hours ECG monitoring belongs to the highly accurate detection method of heart arrhythmias, including PAF. However, before AF paroxysm of occurs, other ECG changes are observed that precede this arrhythmia. If they are identified, the risk of PAF in the patient is higher. Primarily, we are referring to supraventricular premature complexes, especially early ones, “P on T” type. To explain this phenomenon, we believe it is important to consider not only the electrophysiological mechanisms, but also the intra-heart hemodynamics, which also play a crucial role in the development PAF. In our previously published works, we studied the role of heart biomechanics and intra-arterial hemodynamics in arrhythmias, including AF [25–27].

When “P on T” type of premature complexes appear on the ECG, the P wave of the extrasystolic complex lands on the descending limb of the T wave. What mechanisms are taking part during this moment in the biomechanical cardiac cycle? At this moment, the atrioventricular valvular leaflets are closed. If an extrasystole occurs, it catches the atria in a state isolated from the ventricles. In response to the electrical stimulus, a kind of isometric contraction of the atria occurs. Blood, remaining incompressible, exerts additional mechanical pressure on the contracting atria, leading to their stretching. Frequent early atrial premature complexes type “P on T” result in repeated mechanical impacts on the walls of the atria, causing further stretching, altering their morphology and thereby leading to the formation of AF.

Importantly, using the advanced imaging techniques, such as and echocardiography or cardiac magnetic resonance (MRI), helps to improve the risk prediction models. These modalities allow for the assessment of left atrial volume and function – parameters that have been linked to PAF. Integrating these imaging-derived metrics into predictive algorithms could enhance risk stratification, ensuring that we prioritize management for high-risk individuals. In light of this, we believe it is promising to study the stiffness of the left atrium using speckle tracking echocardiography as an additional marker for PAF. In our research, we are planning to include these parameters in our further publications.

As the early “P on T” premature ectopic complexes ($p<0.0001$) are the most significant risk predictor, the patients who have these kind of arrhythmia are highly possible to have already AF paroxysms, not diagnosed. So, to this category of patients can be recommended to perform three days or seven days long ECG monitoring to reveal the arrhythmia.

We believe that the results of our study will contribute to the development of personalized treatment strategies for patients with “P on T” type extrasystoles or PAF initiated by them. Concept of PAF pathophysiological mechanisms will undergo a transformation, taking into account the biomechanical cardiac cycle. Further application of new approaches of risk stratification in clinical practice could provide new data for formulating new strategies for the AF prevention.

Limitations

1) The study is single-center, case-control design. This design introduces a significant risk of selection bias, as the recruited cases (patients with PAF) and controls may not be fully representative of the broader population. The specific practices, patient demographics, and referral patterns of our center limit the generalizability of our results.

2) Limited cohort size, particularly of patients with PAF. Despite the primary cohort included 6,630 patients, in the PAF group it were included 97 of them. A small sample size, particularly of the outcome group, reduces the statistical power of the study. This increases the likelihood of Type II errors (failing to identify true predictor variables) and limits the complexity of the predictive model that can be reliably developed.

3) Potential for model overfitting, as suggested by high AUC. An overfitted model performs well on the data it was trained on but is likely to perform poorly and, greatly diminishing its clinical utility.

4) Lack of external validation. The predictive model was only validated internally using techniques like cross-validation on the original dataset. Internal validation, while valuable, is insufficient to prove the model's robustness and general applicability. This is the most critical step required to transition a research model into a clinically usable tool, and its absence is a major limitation.

In summary, these limitations collectively urge caution in interpreting the model's performance as definitive. The findings should be considered hypothesis-generating. Future prospective, multi-center studies with larger, more diverse cohorts and rigorous external validation are essential to confirm the model's validity and assess its true potential for clinical deployment.

Conclusion

The final regression equation, based on the evaluation of data from 24-hours Holter ECG monitoring, incorporates the following criteria: gender, the number of atrial and atrioventricular supraventricular complexes, the count of single and paired ventricular complexes, variations in rhythms with ventricular complexes, as well as the presence or absence of early "P on T" complexes (AUC=0.996).

We believe that the proposed predictive model appears promising. However, it requires validation in larger cohorts and preferably in prospective or randomized studies before clinical implementation. In the future, it can be helpful to use of the proposed “Arfa” equation in the everyday clinical work of general practitioners, cardiologists and vascular surgeons as the tool that can be easily implemented as the desktop calculator.

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