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Noninvasive risk factors for the prediction of inducibility on programmed ventricular stimulation in post-myocardial infarction patients with an ejection fraction ≥40% at risk for sudden cardiac arrest: Insights from the PRESERVE-EF study

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Abstract

Background: In the PRESERVE-EF study, a two-step sudden cardiac death (SCD) risk stratification approach to detect post-myocardial infarction (MI) patients with left ventricle ejection fraction (LVEF) ≥40% at risk for major arrhythmic events (MAEs) was used. Seven noninvasive risk factors (NIRFs) were extracted from a 24-h ambulatory electrocardiography (AECG) and a 45-min resting recording. Patients with at least one NIRF present were referred for invasive programmed ventricular stimulation (PVS) and inducible patients received an Implantable Cardioverter - Defibrillator (ICD).

Methods: In the present study, we evaluated the performance of the NIRFs, as they were described in the PRESERVE-EF study protocol, in predicting a positive PVS. In the PRESERVE-EF study, 152 out of 575 patients underwent PVS and 41 of them were inducible. For the present analysis, data from these 152 patients were analyzed.

Results: Among the NIRFs examined, the presence of signal averaged ECG-late potentials (SAECG-LPs) ≥ 2/3 and non-sustained ventricular tachycardia (NSVT) ≥1 eposode/24 h cutoff points were important predictors of a positive PVS study, demonstrating in the logistic regression analysis odds ratios 2.285 ($p = .027$) and 2.867 ($p = .006$), respectively. A simple risk score based on the above cutoff points in combination with LVEF < 50% presented high sensitivity but low specificity for a positive PVS.

Conclusion: Cutoff points of NSVT ≥ 1 episode/24 h and SAECG-LPs ≥ 2/3 in combination with a LVEF < 50% were important predictors of inducibility. However, the final decision for an ICD implantation should be based on a positive PVS, which is irreplaceable in risk stratification.

KEYWORDS
cardiac arrest/sudden cardiac death, Holter/event recorders, signal-averaged ECG, ventricular tachycardia/fibrillation

1 | INTRODUCTION

Current guidelines suggest the prophylactic use of an implantable cardioverter-defibrillator (ICD) in post-myocardial infarction (MI) patients with left ventricular ejection fraction (LVEF) ≤ 35% for primary prevention of sudden cardiac death (SCD) (Al-Khatib et al., 2018; Priori et al., 2015). However, the vast majority (approximately 85%) of post-MI patients maintain a preserved LVEF (≥40%) (Serrao et al., 2018), while the annual incidence of sudden cardiac death (SCD) in this group of patients is about 1% (Gorgels & Gijsbers, 2003; Ikeda et al., 2006; Stecker et al., 2006). It is obvious, therefore, that the absolute number of patients who are in danger for SCD in the group of post-MI patients with preserved LVEF is higher compared with the group of patients with reduced LVEF (Makikallio et al., 2005).

In the absence of an adequate risk stratification method and guideline recommendation for primary prevention, the PRESERVE-EF study (Gatzoulis et al., 2019) proposes a two-step SCD risk stratification approach to detect post-MI patients with a LVEF ≥ 40% at risk for major arrhythmic events. Seven non-invasive risk factors (NIRFs) were extracted from 24-h ambulatory electrocardiography (AECG) and a 45-min resting electrocardiography. Patients with at least one NIRF present were referred for invasive programmed ventricular stimulation (PVS). Inducible patients received an ICD.

In this post hoc analysis of the PRESERVE-EF study, the primary goal was to assess the performance of NIRFs extracted from 24-h ambulatory electrocardiography (AECG) and from the 45-min electrocardiographic resting recording in predicting a positive PVS.

2 | METHODS

PRESERVE-EF study enrolled 575 consecutive post-MI patients, on optimal tolerated medical therapy, in seven hospitals in Greece and proposed a two-step arrhythmic risk stratification approach, which effectively detects (sensitivity 100%, specificity 93.8%, positive predictive value 22%, and negative predictive value 100%) a subpopulation of post-MI patients with preserved LVEF at risk for major arrhythmic events (MAEs) that can be effectively addressed with an ICD (Gatzoulis et al., 2019).

In the PRESERVE-EF study, seven electrocardiographic NIRFs were evaluated, at least 40 days after the MI and after any active myocardial ischemia had been excluded (following negative myocardial scintigraphy/exercise treadmill test/stress echocardiography in the previous 6 months) and were considered positive according to the following criteria as they were described in the study protocol: (a) ≥2/3 positive criteria for signal averaged ECG-late potentials (SAECG-LPs), either conventional or modified on a 45-min electrocardiographic recording during resting (Breithart et al., 1991; Gatzoulis et al., 1995), (b) ≥30 premature ventricular complexes (PVCs)/hour on a 24-h ambulatory electrocardiography (AECG), (c) presence of at least one non-sustained ventricular tachycardia episode (≥1 NSVT episode/24 h) on a 24-h ambulatory electrocardiography (Buxton et al., 2000), (d) standard deviation of normal RR intervals (SDNN) ≤75 ms on a 24-h ambulatory electrocardiography (La Rovere et al., 2001), (e) QTc derived from a 24-h ambulatory electrocardiography >440 ms (men) or >450 ms (women), calculated by using the Fridericia formula (Arsenos et al., 2011), (f) combined deceleration capacity (DC) ≤4.5 ms and heart rate turbulence onset (To) ≥0% and heart rate turbulence slope (Ts) ≤2.5 ms (DC ≤ 4.5 ms/To ≥ 0%/Ts ≤ 2.5 ms) on a 24-h ambulatory electrocardiography (Bauer et al., 2009), and (g) ambulatory T-wave alternans (TWA) ≥65 μV in two Holter recording channels, on a 24-h ambulatory electrocardiography (Verrier et al., 2011). The complete study design can be found in the proposed PRESERVE-EF manuscript (Gatzoulis et al., 2014).

The CardioMem CM 4000 Multi-channel ECG Recorder (GE Healthcare) was used for the recordings, and the CardioDay 2.4 (GE Healthcare) software was used for the analysis.

In the presence of at least one NIRF, patients underwent invasive PVS. As per the PRESERVE-EF protocol, stimuli were introduced in two right ventricular sites (apex and outflow tract) at two drive train cycle lengths (550 and 400 ms) at each site. Up to three extra-systoles were introduced after the drive train at each drive train cycle length with coupling intervals progressively (10 ms increments) shortened down to 200 ms or until refractoriness was reached, starting from the last extra-systole. Patients were classified as inducible, if sustained monomorphic ventricular tachycardia or ventricular flutter or polymorphic ventricular tachycardia degenerated into ventricular fibrillation were induced.

Two hundred and four (204) patients had at least one NIRF and therefore an indication for PVS. Fifty-two (52) of them denied the investigation. Finally, 41 out of 152 patients who underwent PVS were inducible.

In the present study, we analyzed data from these 152 patients.

2.1 | Statistical analysis

Data ware analyzed using the statistical package SPSS version 25 (IBM Corp). The Kolmogorov–Smirnov test was used in order to assess normality of distribution for all continuous variables. The variables are not normally distributed and non-parametric test was chosen. To describe the sample, descriptive statistics such as mean, standard deviation, absolute number, and percentages were performed. Continuous variables compared by Mann–Whitney and categorical variables by Pearson's chi-squared test (χ^2). A logistic regression analysis was conducted in order to find prognostic factors

for a patient's ranking in the PVS (+) group. Moreover, a ROC analysis was conducted and the area under the ROC curve (AUC) was interpreted as the probability of correctly identifying whether or not patients are classified into PVS (+) group, based on their profile. A level of significance of <.05 was used in all instances.

3 | RESULTS

The clinical and laboratory characteristics of the sample are presented in Table 1. The majority of the patients were male, smoker, suffered from hypertension, dyslipidemia, receiving B-blockers, ACE or ARBs, Aspirin, P2Y12 inhibitors, and Statin. The mean age of the patients was 60.37 ± 10.1 years old and their mean BMI was 27.7 ± 4.2 kg/m^2. As far as the myocardial infarction type is concerned, STEMI was predominant (62%) and LAD was the culprit vessel in 56.7% (85) of the cases.

Comparing the clinical and laboratory characteristics between PVS-inducible and non-inducible patients, statistically significant differences were found (Table 1). More specifically, 97.56% of PVS (+) were male in comparison to the 86.49% of the PVS (–) group ($p = .048$), 36.6% of PVS (+) patients suffered from diabetes than 15.6% PVS (–) patients ($p = .005$), and 36.6% of PVS (+) patients stated hereditary CAD compared to only 17.3% of PVS (–) patients ($p = .012$). The inducible group demonstrated also statistically significant differences in the use of diuretics and MRAs, compared to the non-inducible group (29.3% vs. 13.6% – $p = .026$ and 29.3% vs. 7.3% – $p = .001$) and differences as far as the STEMI incidence and the LVEF were also detected (82.9% vs. 54.1% – $p = .001$ and 45.6 ± 4.9% vs. 51.1 ± 7.1 – $p = .001$). As far as the electrocardiographic characteristics are concerned, the inducible group demonstrated significantly more prolonged filtered QRS (115.35 ± 23.5 vs. 103.7 ± 19.1 – $p = .045$), while more non-sustained ventricular tachycardia (NSVT) episodes were detected than among the non-inducible patients ($p = .003$).

Table 2 demonstrates the differences in prevalence of the selected NIRFs, derived from the 24-h AECG and from the 45-min resting electrocardiogram, between the two groups. There were statistically significant differences, as far as the prevalence of the cutoffs SAECG-LPs ≥ 2/3 and the NSVT ≥ 1 eposode/24 h is concerned. More specifically, 51.2% of the inducible patients demonstrated SAECG-LPs ≥ 2/3 ($p = .026$), while 46.3% of them had at least one NSVT episode in the 24-h AECG ($p = .006$).

Table 3 presents the logistic regression analysis. The dependent variable was the inducibility in PVS, and as independent variables, the selected NIRFs were chosen. The logistic regression analysis demonstrated that the cutoffs of SAECG-LPs ≥ 2/3 and the NSVT ≥ 1 eposode/24 h were considered to be statistically significant predictors of the inducibility in PVS. More specifically, inducible patients were 2.3 times (odds ratio = 2.285, 95% CI = 1.096 to 4.764, $p = .027$) more likely to demonstrate SAECG-LPs ≥2/3 and 2.9 times (odds ratio = 2.867, 95% CI = 1.342 to 6.128, $p = .006$) more likely to demonstrate at least one NSVT episode per 24 h.

Finally, a simple risk score consisting of the predictors' cutoff values (SAECG-LPs ≥ 2/3 and NSVT ≥ 1 episode/24 h) and a LVEF < 50% was built. Our score achieved odds ratio 14.146 (sensitivity 97%, specificity 26%, $p = .01$) and area under the ROC (AUC) 0.69 for inducibility on PVS (Table 4; Figure 1).

4 | DISCUSSION

The purpose of this study was to address the capability of the predetermined NIRFs in predicting the outcome of the PVS in the PRESERVE-EF cohort.

The main findings are the following: (a) There are statistically significant differences between the inducible and the non-inducible group, as far as baseline clinicolaboratory and electrocardiographic characteristics are concerned. (b) Cutoff points of NSVT ≥ 1 episode/24 h and presence of SAECG-LPs ≥ 2/3 are important risk indicators for a positive PVS, but they can only modestly predict inducibility. (c) The final decision for an ICD implantation should be based on a positive PVS which was irreplaceable in the risk stratification among our examined patient population.

It is well documented that cardiac arrest due to ventricular arrhythmias in the late post-MI phase is the result of the interplay between a susceptible myocardial substrate and the presence of specific triggers. Risk stratification schemes are based on markers that, by identifying the vulnerable substrate and the presence of a provocative condition, are considered to quantify the risk of SCD (Arsenos et al., 2013). Briefly, such markers reflect myocardial substrate lesions and post-infarction fibrosis along with abnormalities in cardiac repolarization and impaired autonomic nervous system function (Arsenos et al., 2013, 2016). Our pre-determined NIRFs have been extensively studied, but none of them can be used alone in guiding prophylactic ICD implantation (Bigger et al., 1984; Exner et al., 2007; Ikeda et al., 2006). Given that a cardiac arrest is likely to be the outcome of a combination of abnormalities, integrating noninvasive test data to improve risk prediction has intuitive appeal (Bauer et al., 2008; Farrell et al., 1991; Gatzoulis, Antoniou, et al., 2017; Gatzoulis, Sideris, et al., 2017; Hohnloser et al., 2004).

Inducible patients suffered from DM more than non-inducible, had more often hereditary CAD, and used diuretics and MRAs more frequently. Furthermore, inducible patients had lower LVEF, more dilated LV and suffered more from STEMI.

Among the tested NIRFs, only NSVT and SAECG-LPs were found to have a statistically significant positive correlation with the inducible PVS. This is easily understandable, since spontaneous NSVT is a potential trigger for VT/VF and SCA and the presence of LPs indicates the existence of an underlying fibrotic and vulnerable myocardial substrate (Gatzoulis et al., 2012). While previously suggested NIRFs like TWA, DC, HRT, HRV, and prolonged QTc were not infrequently met among our PRESERVE-EF population, they were not able to predict VT/VF inducibility. Indeed, another limited noninvasive ECG protocol consisting of only three NIRFs equally predicted of major arrhythmic events (MAEs) in a recently published

TABLE 1 Clinical and laboratory characteristics of the patients

Characteristics	All ($N = 152$)	PVS+ ($N = 41$)	PVS− ($N = 111$)	*p* Value
Age (years)	60.37 ± 10.1	61.73 ± 9.1	59.85 ± 10.4	.308
Male gender (%)	89.47 (136)	97.56 (40)	86.49 (96)	.048
Diabetes mellitus (%)	21.3 (32)	36.6 (15)	15.6 (17)	.005
Hypertension (%)	58 (87)	63.4 (26)	56 (61)	.410
Dyslipidemia (%)	66 (99)	68.3 (28)	65.1 (71)	.716
Smoking (%)	52.7 (79)	53.7 (22)	52.3 (57)	.881
Hereditary SCD (%)	4.7 (7)	4.9 (2)	4.6 (5)	.940
Hereditary CAD (%)	22.5 (34)	36.6 (15)	17.3 (19)	.012
BMI (kg/m^2)	27.7 ± 4.2	27.25 ± 3.5	28.15 ± 4.9	.213
b-Blockers (% yes)	91 (137)	90.24 (37)	91 (100)	.900
ACE or ARBs (% yes)	72.85 (110)	80.5 (33)	70 (77)	.197
Aspirin (% yes)	96.7 (146)	95.1 (39)	97.3 (107)	.511
P2Y12 inhibitors (% yes)	86.8 (131)	80.5 (33)	89.1 (98)	.165
Statin (% yes)	95.4 (144)	100 (41)	93.6 (103)	.098
Diuretics (% yes)	17.9 (27)	29.3 (12)	13.6 (15)	.026
CCBs (% yes)	14.1 (21)	14.6 (6)	13.9 (15)	.907
MRAs (% yes)	13.3 (20)	29.3 (12)	7.3 (8)	.001
LVEF (%)	49.6 ± 7	45.6 ± 4.9	51.1 ± 7.1	.001
LVEDD (mm)	51.4 ± 6	53.25 ± 6.3	50.7 ± 5.7	.021
STEMI (%)	62 (93)	82.9 (34)	54.1 (59)	.001
One-VD (% yes)	60.7 (91)	53.7 (22)	63.3 (69)	.478
LAD (% yes)	56.7 (85)	58.5 (24)	56 (61)	.777
LCx (% yes)	46.7 (70)	46.3 (19)	46.8 (51)	.961
RCA (% yes)	54 (81)	63.4 (26)	50.5 (55)	.156
AECG characteristics				
QRS (ms)	93.66 ± 20.74	92.94 ± 22.6	93.92 ± 20.1	.812
f-QRS (ms)	106.66 ± 20.86	115.35 ± 23.5	103.7 ± 19.1	.045
LAS (ms)	61.13 ± 269.99	67.13 ± 312.5	43.47 ± 19.8	.072
RMS 40 (μV)	34.76 ± 27.24	26.27 ± 23.8	37.64 ± 27.8	.013
NSVT (total No)	0.89 ± 3.69	1.73 ± 4.98	0.56 ± 3.01	.003
PVCs (total No)	2126.34 ± 4923.68	1583.9 ± 4288.4	2329.8 ± 5146.3	.628
SDNN (ms)	123.25 ± 44.82	117.42 ± 40.8	125.35 ± 40.2	.376
QTc (ms)	463.15 ± 24.30	438.92 ± 22.96	435.12 ± 24.82	.552
DC (ms)	2.50 ± 9.59	2.15 ± 11	2.63 ± 9.1	.799
HRTo (%)	−0.01 ± 0.02	−0.01 ± 0.02	−0.02 ± 0.03	.544
HRTs (ms)	6.96 ± 5.36	6.79 ± 4.59	7.02 ± 5.67	.832
TWA ≥65 μV (%)	21.5 (32)	24.4 (10)	20.4 (22)	.594

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; DC, deceleration capacity; fQRS, filtered QRS; HRTo, heart rate turbulence onset; HRTs, heart rate turbulence slope; LAD, left anterior descending artery; LAS, low amplitude (<40 μV) signal duration; LCX, circumflex artery; LPS, late potentials; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NSVT, non-sustained ventricular tachycardia; One-VD, one vessel disease; PVCs, premature ventricular complexes; QTc, corrected QT interval; RCA, right coronary artery; RMS, terminal (last 40 ms) QRS root means square voltage; SDNN, standard deviation of normal to normal heartbeat; STEMI, ST-segment elevation myocardial infarction; TWA, T-wave alternans.

TABLE 2 Prevalence of the selected NIRFs between the PVS inducible and non-inducible patients

Noninvasive risk factors	All patients (*N* = 152)	PVS+ (*N* = 41)	PVS− (*N* = 111)	*p* Value
PVCs ≥30/h (% yes)	35.5% (54)	39% (16)	34.9% (39)	.636
NSVT ≥1 episode/24 h (% yes)	28.9% (44)	46.3% (19)	23.1% (25)	**.006**
SAECG-LPs ≥2/3 (% yes)	36.2% (55)	51.2% (21)	31.5% (34)	.026
QTc >440 (M)/450 (F) ms (% yes)	37.5% (57)	36.6% (15)	40.4% (42)	.673
TWA ≥65 μV (% yes)	21.1% (32)	24.4% (10)	20.4% (22)	.594
SDNN ≤75 ms (% yes)	8.6% (13)	9.8% (4)	8.3% (9)	.783
DC ≤4.5 ms/To ≥0%/Ts ≤2.5 ms (% yes)	9.2% (14)	9.8% (4)	9.3% (10)	.939

Abbreviations: DC, deceleration capacity; NSVT, non-sustained ventricular tachycardia; PVCs, premature ventricular complexes; QTc, corrected QT interval; SAECG-LPS, Signal averaged ECG-late potentials; SDNN, standard deviation of normal-to-normal heartbeat; TO, turbulence onset; TS, turbulence slope; TWA, T-wave alternans.

TABLE 3 Logistic regression analysis for the predictors of PVS inducibility

Predictors	Odds ratio	95% Confidence intervals	*p* Value
PVCs ≥30/h	1.196	0.570–2.509	.636
NSVT ≥1 episode/24 h	2.867	1.342–6.128	.007
LPs ≥2/3	2.285	1.096–4.765	.027
QTc >440 (M)/450 (F) ms	0.852	0.404–1.797	.852
TWA ≥65 μV	1.261	0.537–2.959	.594
SDNN ≤75 ms	1.189	0.345–4.096	.784
DC ≤4.5 ms/To ≥0%/Ts ≤2.5 ms	1.049	0.310–3.551	.939

Abbreviations: DC, deceleration capacity; NSVT, non-sustained ventricular tachycardia; PVCs, premature ventricular complexes; QTc, corrected QT interval; SAECG-LPS, Signal averaged ECG-late potentials; SDNN, standard deviation of normal-to-normal heartbeat; TO, turbulence onset; TS, turbulence slope; TWA, T-wave alternans.

TABLE 4 Combined predictors performance

Variable	Odds ratio	*p* Value	Sensitivity (%)	Specificity (%)	AUC
LVEF <50%	10.734	.001	97	26	0.69
SAECG-LPs ≥2/3	2.285	.027	51	68	0.59
NSVT ≥1 episode/24 h	2.867	.007	46	76	0.61
Risk Score	14.146	.010	97	26	0.69

Note: Odds Ratios, *p* values, sensitivity, specificity, and areas under ROC curves (AUC) for the inducibility endpoint. Risk Score, LVEF < 50% + SAECG-LPs ≥ 2/3 + NSVT ≥ 1 episode/24 h.

Abbreviations: LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; SAECG-LPS, Signal averaged ECG-late potentials.

group of heart failure patients with mid-range LVEF, when the two steps with simplified NIRFs EP inclusive approach was applied (Arsenos et al., 2020).

The LVEF demonstrated statistically significant difference between the inducible and non-inducible group. Indeed, 93% of the inducible patients had LVEF < 50% ($p < 0.001$), and we assumed that by combining the cutoff points of NSVT ≥ 1 episode/24 h, SAECG-LPs ≥ 2/3, and additionally LVEF < 50% in a simple risk score, we could more accurately predict the outcome of the PVS. We demonstrated that this score can predict the inducibility with high sensitivity (97%), but low specificity (26%).

It should be mentioned that we did not systematically examine the performance of cardiac magnetic resonance (CMR) findings among our post-MI patients with rather well-maintained LVEF, a technique that has been suggested to both correlate VT/VF inducibility and an adverse long-term outcome among such patients (Gatzoulis, Antoniou, et al., 2017; Kariki et al., 2020; Yalin et al., 2014).

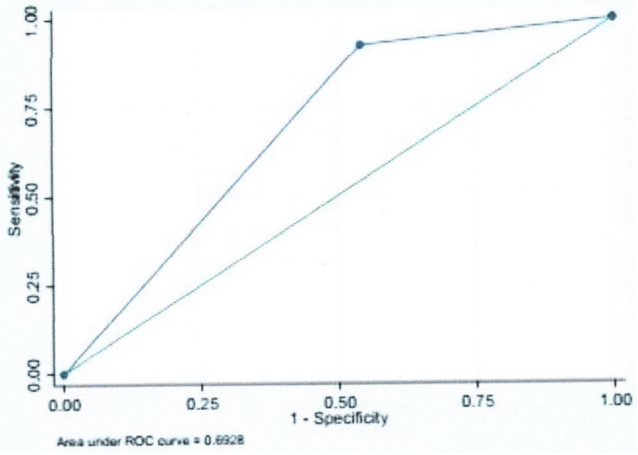

FIGURE 1 RISK score: left ventricle ejection fraction (LVEF) < 50% and non- sustained ventricular tachycardia (NSVT) ≥ 1episode/24h and signal averaged ECG-late potentials (SAECG-LPs) ≥ 2/3

4.1 | Limitations

Not all post-MI PRESERVE-EF patients with at least one NIRF present underwent PVS, due to either patients' preference or/and to primary physician's suggestion. Furthermore, the per protocol incorporation of VF induction on PVS might have falsely increased the supposedly truly high-risk post-MI patients' population.

5 | CONCLUSION

Cutoff points of NSVT ≥ 1 episode/24 h and the presence of SAECG-LPs ≥ 2/3 were considered important predictors of inducibility, implying that post-MI patients presenting them might be at increased risk for future MAEs, despite their relatively preserved LVEF. Furthermore, the combination of these NIRFs with a cutoff LVEF < 50% into a simple score might be useful in further arrhythmic stratification of post-MI patients with mid-range LVEF heart failure. However, the final decision for an ICD implantation should be based on a positive PVS which is irreplaceable in the risk stratification process of the late post-MI phase of a further increasing patient population in the era of primary PCI.

CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

Hereby, I, Konstantinos A. Gatzoulis, consciously assure that for the manuscript *"Noninvasive Risk Factors for The Prediction of Inducibility on Programmed Ventricular Stimulation in Post-Myocardial Infarction Patients with an Ejection Fraction ≥40% at Risk for Sudden Cardiac Arrest. Insights from the PRESERVE – EF Study"* the following is fulfilled: This post hoc analysis was approved by the Ethical Committee of the Hippokrateion General Hospital, Athens, Greece, and followed the ethical Declaration of Helsinki. Patients gave informed consent for their participation.

AUTHOR CONTRIBUTIONS

K.G, P.A, D.T and C-K.A conceived of the presented idea. S.S, P.D, M.E, E.K, P.F, V.V, A.S and P.K developed the theory and performed the computations. K.T, K.T, I.X, and K.T collected the data. D.T, K.T and K.G verified the analytical methods. K.T wrote the manuscript with support from K.G and P.A. All authors discussed the results and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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