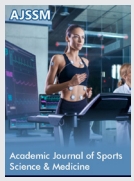

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Analysis Of Plasma D-Dimer Behavior After A HIIT Session By Machine Learning Exploratory Technique

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Abstract

Sport omics has sought to understand immunometabolism. Fifteen athletes of MMA were submitted to HIIT to evaluate acute stress and the kinetics of D-dimer. After applying the Euclidean dissimilarity measure, two dendrograms were proposed that presented three clusters of d-dimer behavior. Cohen's d and r were calculated for the three clusters formed, confirming the choice. The network plot with the Fruchterman algorithm identified that the cluster formed by athletes 4, 7, 15, and 16 had a more differentiated behavior than the other two clusters. The D-dimer does not show similar kinetics, even in a highly homogeneous group subjected to the same type, time, and intensity of stress, presenting itself as a potentially more sensitive biomarker for stress, going far beyond a vascular marker, as perceived during the COVID-19 pandemic. The use of exploratory machine learning techniques for analysis D-Dimer has been suggested since its behavior is highly individual, not allowing analysis only by means.

Keywords: Sportomics; Data mining; Sports Medicine

Introduction

Sportomics science has attempted to explain the interactions between metabolism and the immune system using physical exercise as a model to address the action of nutritional supplements and medications, immunometabolic alterations caused by different forms of sport and in different populations, and the suggestion of different views and biomarkers aiming toward a holistic analysis in data science in the biomedical field [1-6]. D-Dimer is a blood-soluble fibrin degradation product that results from the degradation of thrombi by the fibrinolytic system [7], since its first studies in the 1970s [8], its dosage has been applied to diagnose pulmonary embolism, deep venous thrombosis, and other problems with coagulation and thrombus formation [9-11]. Later, D-Dimer was associated with the degree of stress caused by surgeries, venous and arterial thrombosis, inflammation, disseminated intravascular coagulation, surgeries, trauma, burns, cancer, infection, sepsis, pregnancy, liver disease, thrombolytic therapy, kidney disease

and diseases cardiovascular, and recently, publications on this biomarker have grown due to its sensitivity for early detection of possible thrombotic cardiovascular events in patients with COVID-19 [12-14].

Sportomics science has evaluated this marker as a potential biomarker for the early detection of exercise-induced rhabdomyolysis [15] or fibrinolysis and hypercoagulability by its practice [16]. Traveling to competitions is expected in the lives of high-level athletes. Exercise alone already causes D-Dimer elevation; when associated with car or plane travel, the combination of exercise and travel increases venous and arterial thrombotic risk. These results may explain the reports of venous thrombosis with air travel after sporting events and the reports of cardiac events in older participants running marathons [17]. However, this elevation is directly associated with the intensity of the exercise. For example, a 30-minute run on a treadmill at 60% VO2Max (Maximum Oxygen Volume) did not raise levels above 500 g/L in any participants [18]. Even sedentary individuals and smokers, when submitted to non-intense exercise, do not reach values superior to 500 µg/L, corroborating the previously said [19]. Furthermore, not even when the exercise is of long duration, the fact of not having high intensity means that the levels do not reach this cited mark [20]. The present study aimed to investigate the kinetics of the D-dimer biomarker using high-intensity interval exercise (HIIT) as a stress model and exploratory machine learning strategies for ordering and clustering the behavior of this variable at different acute collection times.

Methods

Subjects

Adult male with a minimum of 5 years of professional experience in MMA competitions and at least 2 years of experience in Cross Combat (High Intensity Interval Training - HIIT). 15 athletes participated in this study [Table 1].

Table 1: Descriptive statistics with position, dispersion and form measures for D-dimer.

	Pre	Post	60 min	120 min
Mean	6.463026533	79.3837668	42.61553473	40.17650221
Standard Error	0.627668915	21.25377372	9.873140244	6.73727225
Median	6.96182	48.958148	36.499073	35.3711525
Mode	2.935	#N/A	#N/A	#N/A
Standard Deviation	2.430951257	82.31551166	38.23850774	25.20856448
Sample Variance	5.909524012	6775.843459	1462.183474	635.4717232
Kurtosis	-1.358021665	1.17598817	0.485125626	-1.361104873
Skewness	-0.221658405	1.313509212	1.074783464	0.444898965
Range	6.965342	274.6573	125.225297	70.266835
Minimum	2.935	7.938588	2.935	12.951568
Maximum	9.900342	282.595888	128.160297	83.218403
Sum	96.945398	1190.756502	639.233021	562.471031
Count	15	15	15	14

Experimental design

The athletes engaged in HIIT (40 min) in an observational and cross-sectional cohort study. All participants rested for 72 h before the exercise protocol. The Combat protocol was individually created to achieve an intensity level of 70% repetition maximum, calculated as previously described [6]. The protocol involved 12 different exercises combined in six modules according to their equivalence.

Blood measurements

Blood samples were collected at the following times: pre-exercise collection (Pre); immediately after exercise (Post); 60 min after the end of exercise (60 min), and 120 min after the end of exercise (120 min). Hematocrit was measured using microhematocrit tubes and centrifugation. The D-dimer level was assessed using ichroma alpha ® (Boditech Med Inc., Gangwon-do, Korea).

Data science and statistics

Descriptive statistics were performed on the data and Shapiro–Wilk normality test. The equal variance test was applied if the Shapiro–Wilk test presented a result indicating a normal distribution ($P>0.05$). For results with $P>0.05$, the paired Student's t test followed; if $P\leq0.05$, the paired Student's t test followed the nonparametric Mann–Whitney test. If the Shapiro–Wilk test presented a result indicating a nonnormal distribution ($P\leq0.05$), the nonparametric Mann–Whitney test was directly applied. Nevertheless, in the phase of the univariate analysis, the one-way dependent repeated-measures ANOVA was performed because they were the same individuals at different moments. Cohen's equations [21] were used to calculate the effect size for hematocrit and d-dimer. Next, the Pearson and Spearman correlation tests were applied. The Spearman correlation was used for a visual analysis using the heatmap strategy and the Pearson test was used as an initial measure for the following machine learning analyses.

Exploratory models of machine learning: CLUSTER - Classical Clustering (Agglomerative Hierarchical Method) and Nearest neighbor (single linkage); ORDINATION – Principal Component Analysis (PCA) and Multiple Correspondence Analysis (MCA). Unsupervised and exploratory machine learning models were applied to classify or group observations and variables, in addition to seeking correlation or association among them. For this, the hierarchical clustering and PCA algorithms were selected for the quantitative study variables (d-dimer) and the MCA was selected for the qualitative or categorical variables (collection times). As initial treatment, the measures of dissimilarity (distance) among the observations of the study variable were calculated, namely, the Quadratic Euclidean, the Euclidean, the Manhattan, and the Canberra [Supp. Table 1-3]. Of these, the results for the last three are shown in [Supplementary Figure 1]. Only the Euclidean dissimilarity measure was used as a standard for analysis and decision-making. The Fruchterman-Reingold algorithm was also applied to distribute vertices uniformly, minimize edge crossings, make edge lengths uniform and reflect inherent symmetry [22]. The Z score was not previously applied because the observations contained similar measurement units. Sigma Plot 14.5 (Academic Perpetual License – Single User – ESD Systat® USA), Past 4.03 (Free version for Windows) and, R 4.2.1® integrated with R Studio® (Free version for Windows) were used to carry out the different statistical tests and produce the graphs.

Supp. Table 1: Subjects' demographic characteristics (n = 15).

	Mean	Median	Range	SD	SE
Age (years)	30.4	29	23-41	5.23	1.35
Mass (kg)	81.5	80	60-108	13.89	3.58
Height (m)	1.77	1.78	1.68-1.84	0.05	0.01
BMI (kg/m2)	25.9	25.6	20.3-33.0	3.46	0.89
BMI – Body Mass Index; SD – Standard Deviation; SE – Standard Error.					

Supp. Table 2: Pairs of observations of distance measurements.

	quadratic Euclidean	Euclidean	Manhattan	Canberra
A1 - A3	6296.68	79.35	109.84	2.44
A1 - A4	64689.8	254.34	363.67	2.11
A1 - A5	5742.77	75.78	84.73	2.01
A1 - A6	9165.71	95.74	182.92	2.02
A1 - A7	29998.94	173.2	357.9	1.96
A1 - A8	6299.52	79.37	151.55	2.23
A1 - A9	7996.78	89.42	153.41	1.94
A1 - A10	7132.93	84.46	118.31	1.85
A1 - A11	6664.18	81.63	163.09	2.64
A1 - A12	4459.05	66.78	99.26	2.13
A1 - A13	7241.52	85.1	113.29	3
A1 - A14	7787.82	88.25	116.5	2.66
A1 - A15	17630.56	132.78	281.76	1.96
A1 - A16	18702.28	136.76	267.82	2.31
A3 - A4	77378.38	278.17	373.46	2.08
A3 - A5	2135.32	46.21	111.4	1.26
A3 - A6	11415.9	106.85	195.62	2.06
A3 - A7	49564.59	222.63	396.52	2.39
A3 - A8	1705.91	41.3	46.85	1.14
A3 - A9	8599	92.73	225.15	2.45
A3 - A10	4861.14	69.72	175.94	2.2
A3 - A11	2855.68	53.44	58.16	1.55
A3 - A12	196.81	14.03	30.39	0.78
A3 - A13	121.43	11.02	23.81	0.99
A3 - A14	146.32	12.1	29.08	0.94

A3 - A15	30377.06	174.29	366.67	2.62
A3 - A16	28656.79	169.28	218.24	2.2
A4 - A5	74313.11	272.6	265.82	1.18
A4 - A6	31166.06	176.54	345.53	0.7
A4 - A7	15711.1	125.34	367.62	0.91
A4 - A8	56801.25	238.33	371.63	2.15
A4 - A9	47794.54	218.62	354.46	1.34
A4 - A10	57533.05	239.86	330.96	1.39
A4 - A11	51533.03	227.01	387.92	2.45
A4 - A12	73714.37	271.5	313.91	1.75
A4 - A13	76954.71	277.41	317.92	2.53
A4 - A14	76969.77	277.43	319.05	2.25
A4 - A15	27052.03	164.48	379.06	1.34
A4 - A16	14161.67	119	444.92	1.49
A5 - A6	9259.21	96.22	143.86	1.02
A5 - A7	41385.36	203.43	330.79	1.51
A5 - A8	3843.47	62	102.66	2.04
A5 - A9	3832.86	61.91	159.42	1.38
A5 - A10	1402.3	37.45	110.21	1.05
A5 - A11	5097.33	71.4	118.96	2.47
A5 - A12	1434.18	37.87	70.82	0.88
A5 - A13	1830.36	42.78	46.24	1.65
A5 - A14	1963.55	44.31	47.99	1.35
A5 - A15	21749.46	147.48	300.94	1.75
A5 - A16	27694.57	166.42	275.86	2.2
A6 - A7	15487.22	124.45	240.98	1.04
A6 - A8	5264.55	72.56	195.26	1.63
A6 - A9	2568.71	50.68	183.79	0.83
A6 - A10	4367.21	66.08	160.29	0.85
A6 - A11	4189.92	64.73	211.56	1.92
A6 - A12	9690.04	98.44	137.55	1.51
A6 - A13	11111	105.41	138.84	2.29
A6 - A14	11227.79	105.96	140.6	2.04
A6 - A15	6934.87	83.28	211.14	0.97
A6 - A16	5667.5	75.28	268.56	1.39
A7 - A8	37087.45	192.58	381.75	2.23
A7 - A9	22270.35	149.23	268.75	1.38
A7 - A10	30356.98	174.23	259.35	1.56
A7 - A11	33979.66	184.34	398.05	2.53
A7 - A12	44614.62	211.22	324.04	2.13
A7 - A13	49686.51	222.9	325.33	2.73
A7 - A14	50338.53	224.36	327.09	2.34
A7 - A15	4067.09	63.77	280.04	0.61
A7 - A16	7353.29	85.75	455.05	1.52
A8 - A9	5770.15	75.96	190.77	1.75
A8 - A10	3761.62	61.33	167.08	1.52
A8 - A11	157.77	12.56	106.05	0.57
A8 - A12	1562.82	39.53	47.66	1.32

A8 - A13	1709.27	41.34	70.51	1.27
A8 - A14	1707.38	41.32	76.39	1.4
A8 - A15	22283.59	149.28	332.3	2.07
A8 - A16	17446.37	132.08	184.08	1.78
A9 - A10	710	26.65	97.48	0.43
A9 - A11	5759.05	75.89	214.28	1.67
A9 - A12	6855.24	82.8	140.27	1.92
A9 - A13	7907.91	88.93	141.56	2.24
A9 - A14	8084.6	89.91	143.31	2.43
A9 - A15	8329.81	91.27	213.83	0.9
A9 - A16	14842.78	121.83	271.28	1.4
A10 - A11	4258.12	65.25	171.83	1.72
A10 - A12	3715.53	60.96	97.82	1.59
A10 - A13	4212.05	64.9	99.11	2.07
A10 - A14	4324.21	65.76	100.87	2.22
A10 - A15	13739.42	117.22	255.69	1.21
A10 - A16	19538.36	139.78	260.97	1.7
A11 - A12	2583.66	50.83	64.77	1.78
A11 - A13	2847.86	53.37	87.62	1.07
A11 - A14	2874.54	53.61	93.5	1.88
A11 - A15	20609.07	143.56	325.59	2.3
A11 - A16	14657.11	121.07	174.03	1.33
A12 - A13	351.81	18.76	13.94	1.35
A12 - A14	468.23	21.64	19.82	1.14
A12 - A15	26392.36	162.46	347.31	2.25
A12 - A16	25908.34	160.96	224.9	1.9
A13 - A14	33.28	5.77	31.26	0.84
A13 - A15	29984.32	173.16	368	2.64
A13 - A16	28962.72	170.18	236	2.05
A14 - A15	30501.83	174.65	365.72	2.49
A14 - A16	29294.79	171.16	235.78	2.53
A15 - A16	8312.3	91.17	404.7	1.41

Supp. Table 3: Values of Effect size.

Effect size	Small	Medium	Large
Cohen r	0.1	0.3	0.5
Cohen d	0.2	0.5	0.8
Source: (Cohen, 1992).			

Ethical approval

The participants received all the information about the study's objectives, procedures, and risks. Only after agreeing to this information were, they invited to sign an informed consent form (TCLE), which assured their rights of privacy and freedom to withdraw from the study when they agreed. The study was previously submitted and approved by the Ethics Committee in Research involving Human Beings of the Federal University of Mato Grosso (UFMT), having been approved under number: 5,716,414.

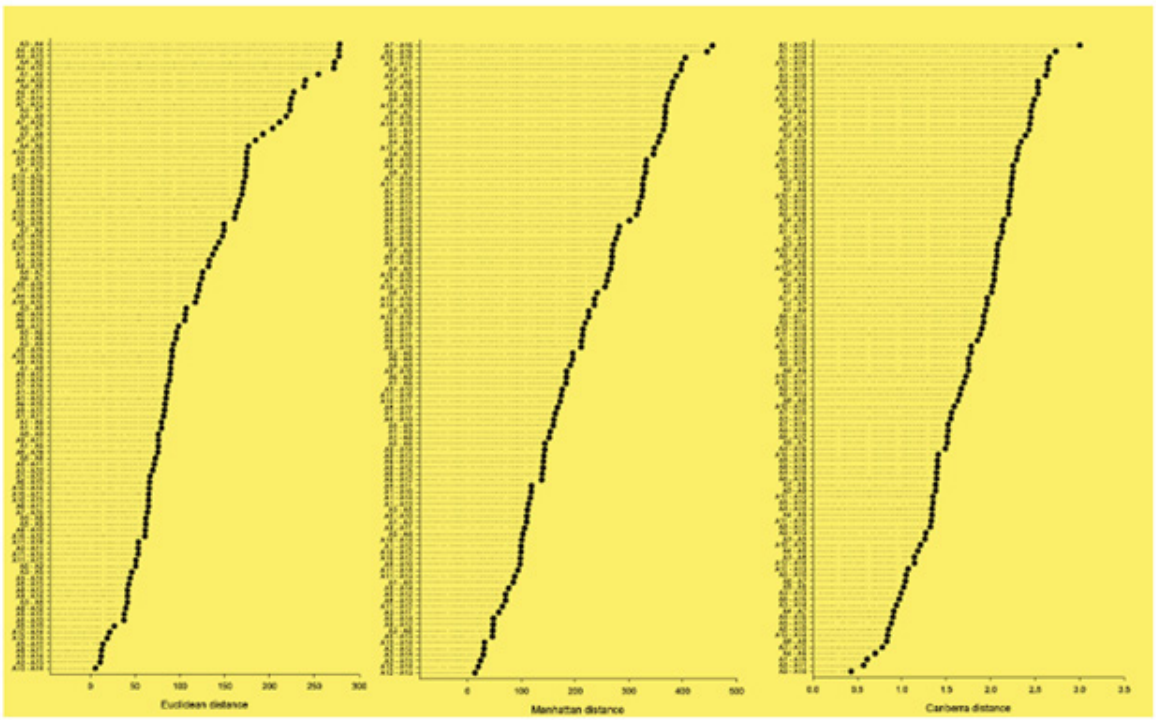
Results

When the first article on the impact of the new training method was published [6], it became clear that the D-dimer biomarker did not have a similar behavior among athletes, even though the sample was extremely homogeneous and submitted to the same kind of stress [Table 2]. This discrepancy led us to conduct an experiment with the same sample, conditions, and exercise method, aiming at a multivariate analysis of this biomarker [Table 1]. presents the descriptive statistics of the observations of the study variable

(d-dimer) being treated with a single group of individuals, aiming at an initial observation of the measures of position, dispersion, and shape. Hematocrit measurement at the same collection times was carried out to control the hydration status of the participants. Any plasma hydration change, whether in hemoconcentration or hemodilution, would require the application of correction factors in the observation of the study variable (d-dimer). As both Student's t test and ANOVA did not identify a significant difference in the hematocrit between the collection times, no adjustment factor was applied to the D-dimer, since its changes were caused by the exercise method and not by changes in plasma hydration.

Table 2: Integrated and holistic statistical analysis on means.

	≠	First choice with T test				For Anova One Way Test				Cohen d	
	Pre	SWT	EVT	MWT	T test	DAG	Holm–Sidak	Tukey	Bonf.	D	r
HT	Post	0.317	0.745	11	0.145		0.074	0.07	0.092	0.55	0.26
	60 min	0.533	0.825	37	0.17	0.04	0.088	0.07	0.092	0.52	0.25
	120 min	0.206	0.71	0	0.225		0.081	0.093	0.126	0.44	0.22
DD	Post	<0.050	<0.050		<0.001		<0.001	<0.001	<0.001	1.25	0.53
	60 min	<0.050	<0.050		0.002	<0.001	0.068	0.102	0.14	1.33	0.55
	120 min	<0.050	<0.050		<0.001		0.074	0.156	0.226	1.88	0.68



Supp. Figure 1: Distance measurements.

After applying the Euclidean measure of dissimilarity, two dendrograms were proposed that presented three possible clusters of d-dimer behavior in the form of classical clustering [Figure 1A] and neighbor joining clustering [Figure 1B]. To confirm the proposed clustering, Cohen's d and r were calculated for the three clusters formed, confirming three different behaviors within the sample [Figure 1C]. The network plot was created from the Euclidean measure of dissimilarity and with the application of the Fruchterman-Reingold algorithm [Figure 2A]. identified that the cluster formed by athletes 4, 7, 15, and 16 had a more differentiated behavior in relation to the other two clusters, which had already been noted in [Figures 1 A/B] and could be identified again in the graph with the results of the principal component analysis [Figure 2B]. The perceptual map with multiple correspondence analysis found an association between collection times prior to stress and those after 120 min, suggesting a rapid recovery of the baseline state for this biomarker [Figure 2C].

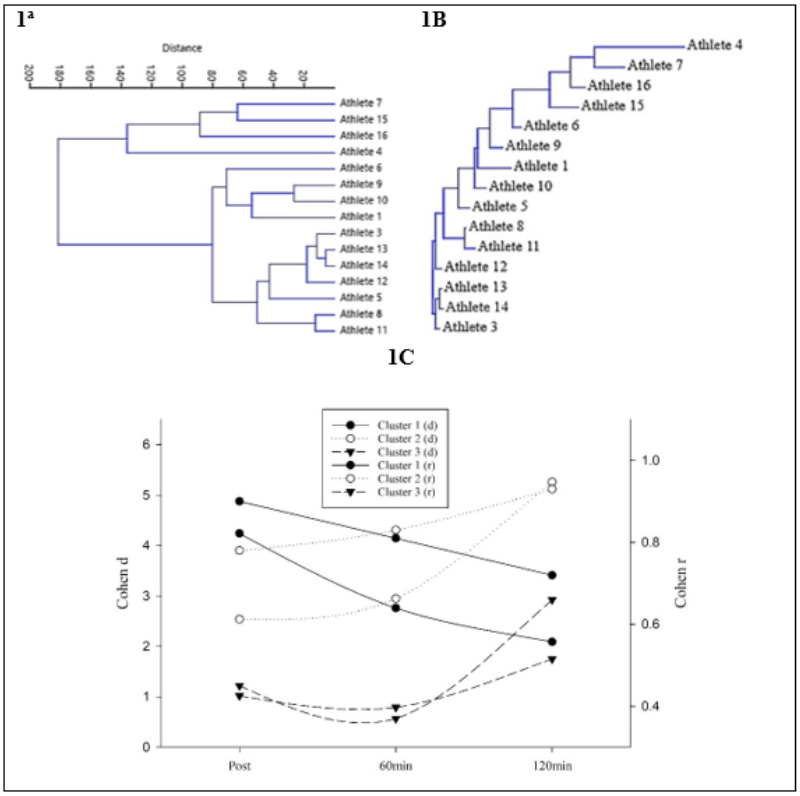


Figure 1: 1A Dendrogram with D-dimer Euclidean similarity index (classical clustering); 1B Dendrogram with Euclidean distance index (neighbor joining clustering); 1C Cohen's effect size calculation corroborated the hypothesis of three distinct kinetics for the d-dimer.

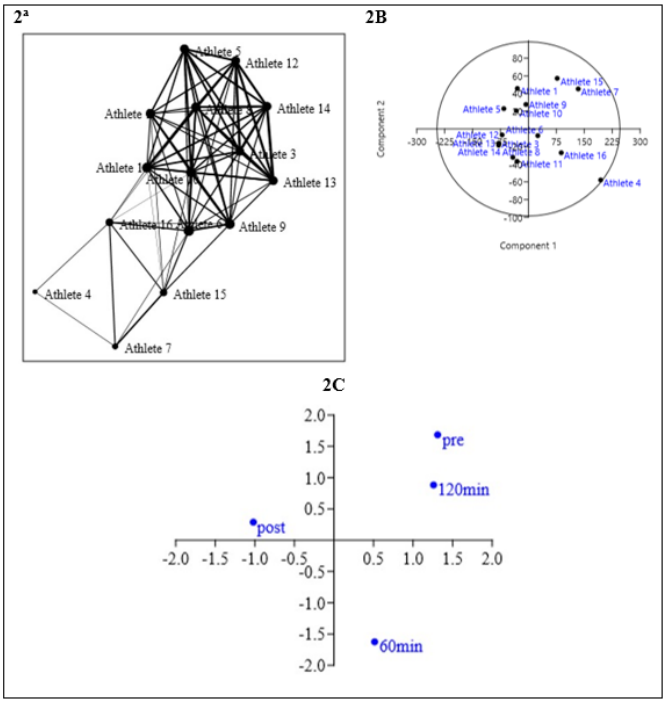


Figure 2: 2A Network plot with the Euclidian similarity index and Fruchterman-Reingold algorithm; 2B Principal component analysis (PCA) confirmed the hypothesis of cluster behavior; 2C The perceptual map of the multiple correspondence analysis (MCA) revealed an association between the collections prior to stress and those after 120 min.

Discussion

D-dimer is a blood-soluble fibrin degradation product that results from the degradation of thrombi by the fibrinolytic system [7]. Since it was first the object of studies in the 1970s [8,9], the dosage of D-dimer has been applied for the diagnosis of pulmonary embolism, deep venous thrombosis, and other problems with coagulation and thrombus formation [10,11]. Later, D-dimer was associated with the degree of stress caused by surgeries. The degree of invasiveness is separated into types I, II, and III (from least to most invasive); their levels increased postoperatively, with type I reaching a peak after 7 days, with a peak not exceeding the normal range (300 µg/L); a peak of (1500 µg/L) for type II, returning to normal values after 25 days; and a peak of (4000 µg/L) for type III, returning to baseline values in 38 days [12]. There are several clinical disorders associated with the elevation of this biomarker, such as venous and arterial thrombosis, inflammation, disseminated intravascular coagulation, surgeries, trauma, burns, cancer, infection, sepsis, pregnancy, liver disease, thrombolytic therapy, kidney disease, and cardiovascular diseases [13].

Recently, publications on this biomarker have grown due to its sensitivity for the early detection of possible thrombotic cardiovascular events in patients with COVID-19 [14,23]. Sports and medical sciences have evaluated this marker as a potential biomarker for early detection of exercise-induced rhabdomyolysis [15] or of fibrinolysis and hypercoagulability by its practice [16]. However, there is scarce information regarding the correlation of this marker with the practice of physical exercise. Traveling to competitions is common in the lives of high-level athletes. Exercise alone causes D-dimer elevation, and when associated with car or plane travel, the combination of exercise and travel increases venous and arterial thrombotic risk. This may explain the reports of venous thrombosis with air travel after sporting events and the reports of cardiac events in older participants running marathons [18]. However, it seems that this elevation is directly associated with the intensity of the exercise. For example, a 30-minute run on a treadmill at 60% VO2Max (maximum oxygen volume) did not raise levels above 500 µg/L in any of the participants [19]. Even sedentary individuals and smokers, when submitted to nonintense exercise, do not reach values above 500 µg/L, corroborating previous reports. Even when the exercise is of long duration, the lack of high intensity means that the levels do not reach this cited mark [20]. Modern science must apply exploratory machine learning strategies to generate holistic and integrated analyses of the results [24].

From the two generated dendrograms [Figures 1 A and B], it is clear that this biomarker has different kinetics, even in highly homogeneous groups submitted to the same type, time, and intensity of stress. It was possible to observe three clusters in the sample with 15 individuals generated from the application of the Euclidean measure of similarity. Data were corroborated by the calculation of Cohen's effect size when evaluated in clusters. This indicates that there is no possibility of evaluating this biomarker by measures of position and dispersion contained in descriptive statistics or the application of univariate analyses. The group formed by Cluster 1 had a sharper peak of D-dimer (Post) with subsequent decay in its concentration; the group formed by Cluster 2 had an increasing trend with a peak in the last collection time (120 min); and the group formed by Cluster 3 had an acute peak (post), a slight decay (60 min) and an increasing trend until its highest concentration (120 min), revealing three different kinetics. [Figure 2A], showing the network plot with the Euclidian similarity index and Fruchterman-Reingold algorithm, showing principal component analysis (PCA), confirm the hypothesis of cluster behavior and explain the behavior by clusters. Finally, [Figure 2C], through the perceptual map of the multiple correspondence analysis (MCA), shows an association between the collection prior to stress and that after 120 min. The present work has new implications and possibilities for the use of D-dimer in sportomics science, with differentiated kinetics in relation to the main clinical disorders.

Conclusion

The D-dimer biomarker does not show similar kinetics, even in a highly homogeneous group and subjected to the same type, time, and intensity of stress, presenting itself as a potentially more sensitive biomarker for immunometabolic stress, and going far beyond a vascular marker, as perceived during the COVID-19 pandemic. The use of multivariate statistics with exploratory machine learning techniques for a holistic and integrated analysis of different experiments with this biomarker is suggested since its behavior is highly individual, not allowing analysis by means and classic univariate statistics.

Highlights:

- D-dimer, a fibrin degradation product traditionally used for diagnosing vascular disease; with the onset of COVID-19, it became clear that this biomarker goes much further.
- Many biomarkers have similar kinetics in homogeneous groups. However, for analytes that do not follow this rule, classical measures of position, dispersion, and statistical methods with univariate analyses do not show adherence.
- The use of multivariate statistics with exploratory machine learning techniques for a holistic and integrated analysis of different experiments with this biomarker is suggested since its behavior is highly individual, not allowing analysis by means and classic univariate statistics.

Funding details

There was no funding for this study.

Data availability statement

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

Author contributions

LCOG and AMMN conceived and designed the study. LCOG, ELF and AMMN collected the data. LCOG, ELF, RJSB, RLN, ACHF, FRCGV and AMMN analyzed the data and wrote the manuscript. All authors read and provided critical feedback on the manuscript prior to approval.

Acknowledgement

None.

Conflict of Interest

The authors report there are no competing interests to declare.

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