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Research article

NOVEL BIOMARKERS FOR CARDIOVASCULAR RISK PREDICTION AMONG PROFESSIONAL DIVERS

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The study relevance is associated with remote negative effects produced by diving on health and related to high fatality rates. Research on cardiovascular risk assessment (CVRA) in divers is scarce. We aimed to evaluate the accuracy of some novel biomarkers versus an established cardiovascular risk estimator in CVRA among professional divers.

A comparative cross-sectional study was conducted on a total of 50 professional divers and an equal number of marine seafarers. Participants were clinically evaluated and subjected to electrocardiography (ECG), basic biochemical analyses, and assessment of some trace metals and oxidative stress biomarkers (OSBMs). Optimal, 10 years, and lifetime CVR was assessed by the Atherosclerotic Cardiovascular Disease (ASCVD) risk estimator. A predictive model for CVR among professional divers was built by testing the performance of some novel biomarkers versus the ASCVD risk estimator.

According to our findings, the professional divers and seafarers showed increased 10 years and lifetime CVD risk compared to the optimal, although the divers were at a higher risk and showed noticeable electrophysiological changes. A proposed model comprising significant CVR predictors and elements of the ASCVD risk estimator improved its performance in CVRA. Corrected QT wave interval was accurate in CVD risk definition and stratification in divers and seafarers (AUC (95 % CI) = 0.692 (0.584–0.800), sensitivity = 60.0 %, specificity = 84.0 %, PPV = 78.9, NPV = 67.7, $p < 0.001$).

Therefore, the CVD risk in divers is quite high and including CVRA in their periodic examinations is crucial. Adding selected biomarkers, particularly ECG changes and some OSBMs with elements of the ASCVD risk estimator improves its accuracy in CVRA.

Keywords: *risk factors, cardiovascular risk estimators, biomarkers, ECG changes, occupational diseases, oxidative stress biomarkers, professional diving.*

Professional divers' tasks expose them to hydrostatic and hyperbaric environments that involve many stresses [1]. This increase in stress levels is multifactorial and could be potentially harmful to the cardiovascular system [2]. Indeed, the unique underwater environment and increased physical efforts, changing hemodynamics (blood pressure and heart rate) and mental stresses during scuba diving are followed by a rise in the production of free radicals, increased oxidative stress (OS) and disturbed trace metal levels that all add to the deleterious effects on the cardiovascular system [3–5]. In addition, water immersion adds thermal stress, which may influence redistribution of the blood flow and volume overload to the compromised heart.

Cardiovascular associated events have been contributing to most of diving-related

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fatalities [6]. Accordingly, cardiovascular risk assessment during fitness evaluation is crucial for identification of patients with high risk of cardiovascular diseases (CVD). Conventional risk assessment tools are commonly utilized either by risk prediction models, risk charts or cardiac stress testing[1]. These decision tools allow early intervention by their users to recommend changes in patients' lifestyles and/or medications. Also, it helps control modifiable CVR factors such as smoking, dyslipidemia, hypertension, diabetes, and obesity [7]. Using cardiovascular risk (CVR) formulae at a population level can be beneficial in surveillance of CVD incidence rates and facilitates target public health interventions [7].

During any enforcement of preventive measures, a global risk approach leads to more accurate estimation of risk and guidance of the clinical primary prevention efforts. Global risk of coronary heart disease (CHD) is defined per calculating the absolute risk of having a CHD event (e.g., death, myocardial infarction) over a certain period. The calculation is based on an empiric equation that combines major risk factors, such as blood pressure and cholesterol levels. The atherosclerosis and cardiovascular diseases (ASCVD) risk estimator depends mainly on the traditional risk factors assessments [8]. It is currently replacing the known Framingham risk score of cardiovascular risk [9]. From the clinical and prevention perspective, there is a demand to improve risk estimation and stratification with robust biomarkers that provide long-term discriminative information better than those available for estimating CVR factors [10]. For instance, the prevalence of some cardiovascular symptoms and diseases may be higher in male former divers than in the general population. Further exploration of novel biomarkers and the recent analytical methods have been mentioned and recommended in many studies [11, 12].

On the other hand, electrocardiogram has been commonly used to determine individuals at high risk of cardiovascular disease. It also predicts those at high risk for certain specific diseases and coronary heart diseases[2]. Professional divers create adaptations to the underwater environmental changes including the myocardium, which may be associated with electrocardiographic (ECG) changes. Pathological ECG findings may offer important clues about structural abnormalities of the heart, that have been identified as possible causes of sudden death in divers [13].

In this context, we proceeded in this study to evaluate some novel biomarkers in CVR assessment among professional divers. This was achieved through investigating conventional as well as novel CVR biomarkers; assessing the validity of ASCVDR estimator and its relation to other biomarkers; and finding the best predictive model for CVR assessment among professional divers.

Materials and methods. The full description of the study population is found in a previous work by our group [14]. Briefly, we conducted a comparative cross-sectional study between June 2017 and May 2018 at the General Naval Hospital in Alexandria. A total of 100 subjects were recruited and assigned into two equal groups (a study group of professional divers (n = 50) and a group of seafarers sharing similar maritime environment except for diving (n = 50)). We used a predesigned interviewing questionnaire to collect background information on divers' sociodemographic data; physical activity and exercise; lifestyle; type of occupational activities; the number of immersions over the last year both as a leisure and occupational activity; average

[1] Harding D.E. Head Off Stress. Beyond the bottom line. London, Shollond Trust Publ., 2009, 336 p.

[2] Kannel W.B., McGee D., Gordon T. A general cardiovascular risk profile: the Framingham Study. *Am. J. Cardiol.*, 1976, vol. 38, no. 1, pp. 46–51. DOI: 10.1016/0002-9149(76)90061-8

and maximum immersion depth and duration; family and individual medical history stating the existing health issues to exclude concomitant diseases.

The study was approved by the institutional review board and the Ethics Committee of the High Institute of Public Health Alexandria University. The research was conducted in accordance with the ethical guidelines of Helsinki's Declaration (2013). Data sheets were coded with numbers to maintain the anonymity and confidentiality of patient's data.

This article does not contain any studies with animals performed by any of the authors.

We informed the enrolled participants about the aims and concerns of the study and how it will add to better understanding of the disease etiology and triggering factors. The participants appreciated the outlined study aims and tasks and were highly motivated to be included in the cohort for long-term clinical observation. However, we did not involve the participants in the study design, or conduct, or dissemination plans of our research. All the laboratory and clinical data were reported to the participants, and we discussed the study findings in a simple language.

All participants signed an informed written consent after explaining the aim and concerns of the study.

All participants were interviewed to get a clear picture of occupational and common diseases and were clinically evaluated for anthropometric measurements and complete general and heart examination. All divers and marine seafarers were subjected to a 12 leads electrocardiography (ECG) to record Rate/min, QRS complex (msec), P-R interval (msec), QT wave (msec), R-R minimum and R-R maximum which is the measurement of the long lead II during deep inspiration and the Sokolov of the precordial chest leads. We used the equation developed by Chenoweth et al., to calculate the corrected QT wave interval [15]:

$$\text{The corrected QT} = \text{QT Interval} / \text{sqr (RR Interval)}$$

Basic biochemical analyses, assessment of some trace metals (Cu+, Fe+, and Zn+) and oxidative stress biomarkers (malonic dialdehyde (MDA), total antioxidant status (TAS), glutathione-S-transferase (GST), glutathione (GSH), glutathione-reductase (GR), glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT)) were done according to the standard procedures.

Cardiovascular risk assessment (CVRA) was done using the ASCVDR estimator Plus developed by the American College of Cardiology (ACC) and American Heart Association (AHA). The ASCVDR estimator Plus calculates the CVR by using the following data: age, sex, race, SBP, DBP, TC (mg/dl), HDL-C(mg/dl), LDL-C(mg/dl), smoking, history of DM, treatment of hypertension, use of statin, and use of aspirin. It estimates the 10 years risk, the life time risk and mentions the optimal risk value for comparison. It could be also used to compare the risk during the follow up of an individual according to the intervention done [16].

Data was revised and fed to computer software (IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp)). The Kolmogorov - Smirnov test was used to verify the normality of distribution. Qualitative data were described using number and percent. Quantitative data that was described using range (minimum and maximum), mean, standard deviation (SD), median and interquartile range (IQR). Significance of the obtained results was judged at the 5 % level. Chi-square test was used for categorical variables, to compare between different groups. Correction of chi-square was done using the Fischer's exact test (FET) when more than 20 % of the cells have expected count less than 5. Student's t-test was used to compare normally distributed quantitative variables between two studied groups. For

abnormally distributed quantitative variables, Mann – Whitney U-test was used to compare between the two studied groups. Pearson coefficient was used to correlate between two normally distributed quantitative variables. To compare between two time periods, Wilcoxon signed ranks test was used for abnormally distributed quantitative variables. Univariate and multivariate binary logistic regression analyses were run to detect the most independent factors/predictors of lifetime, 10 years, and optimal CVD risk. A multivariate binary logistic regression model was built to infer the predicting value, it was used to draw the Receiver Operator Characteristic (ROC) curve and define the area under the curve (AUC). *P* value < 0.05 was set as a level of significance.

Results and discussion. The comparison of the ASCVD risk score between the two studied groups showed that the mean lifetime and the 10 years CVD risk were higher in the professional divers than the controls (46.36 ± 8.75 and 3.62 ± 2.29, $p = 0.081$ vs 40.72 ± 13.99 and 2.68 ± 2.09, $p = 0.009$ respectively). On the other hand, the mean optimal CVR score did not differ significantly between the two groups (0.63 ± 0.27 vs 0.68 ± 0.49 respectively; $p = 0.637$). The 10 years CVD risk was higher than optimal risk with a % change of 74.01 ± 20.35 for the diver and 66.89 ± 17.70 for the marine seafarers (Table 1).

The ROC curve in Figure 1 was built to select the best biomarkers in predicting the optimal, 10 years and lifetime CVD risks. The AUC for the different CVD risks was low (AUC = 0.523, 0.543, and 0.548, respectively $p > 0.05$).

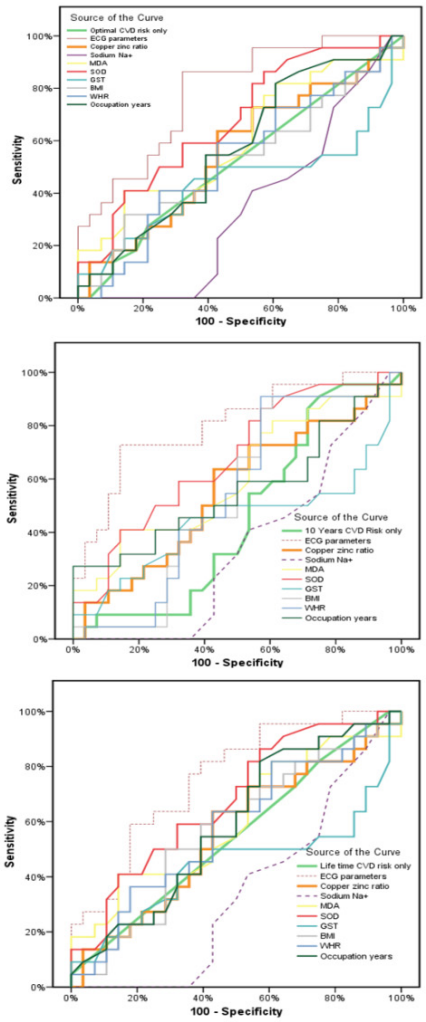
Consistently, ECG changes and serum SOD enzyme level were significant predictors of the optimal, 10 years and lifetime CVD risks as inferred by ASCVD risk estimator ($p < 0.05$). The other tested parameters including BMI, WHtR, serum Na+, serum Cu/Zn ratio, GST, MDA as well as the duration of employment showed poor performance in predicting the CVD risk ($p > 0.05$).

Table 1

Atherosclerosis Cardiovascular Diseases (ASCVD) risk scores among the enrolled divers and marine seafarers

Cardiovascular Disease Risk (Mean ± *SD*)	Divers ($n = 50$)	Marine seafarers ($n = 50$)	Significance	Validity of differences *(p)*
Lifetime CVD risk	46.36 ± 8.75	40.72 ± 13.99	$t = 2.417^*$	0.018^*
10 years CVD risk	3.62 ± 2.29	2.68 ± 2.09	$U = 872.0^*$	0.009^*
Optimal CVD risk	0.63 ± 0.27	0.68 ± 0.49	$U = 1196.5$	0.637
Difference	2.99 ± 2.17	2.01 ± 1.74	$U = 885.5^*$	0.012^*
% Changes	74.01 ± 20.35	66.89 ± 17.70	$U = 850.0^*$	0.006^*
CVD risk (Mean ± *SD*)	Optimal CVD risk	10 years CVD risk		
Divers ($n = 50$)	0.63 ± 0.27	3.62 ± 2.29	$Z = 6.155^*$	$< 0.001^*$
Difference	2.99 ± 2.17			
% Changes	74.01 ± 20.35			
Marine seafarers ($n = 50$)	0.68 ± 0.49	2.68 ± 2.09	6.155^*	$< 0.001^*$
Difference	2.01 ± 1.74			
% Changes	66.89 ± 17.70			

Note: CVD is cardiovascular diseases; *t* – Student's *t*-test; *U* – Mann – Whitney test; *Z* – Wilcoxon signed ranks test; *p* value for comparing between optimal CVD Risk and 10 Years CVD Risk in each group; * – statistically significant at $p \leq 0.05$.



		CVD Risk					
		AUC	p-value	Sensitivity (%)	Specificity (%)	PPV	NPV
Optimal CVD Risk~	Optimal CVD risk only	0.523	0.784	27.27	78.57	50.0	57.9
	ECG parameters	0.795	<0.001*	77.27	75.0	70.8	80.8
	Copper zinc ratio	0.555	0.506	63.64	57.1	53.8	66.7
	Sodium Na^+	0.654	0.063	90.91	42.9	55.6	85.7
	MDA	0.605	0.207	40.91	85.7	69.2	64.9
	SOD	0.677	0.033*	86.36	42.9	54.3	80.0
	GST	0.555	0.506	45.45	85.7	71.4	66.7
	BMI	0.528	0.740	54.55	60.7	52.2	63.0
	WHR	0.531	0.710	59.09	57.1	52.0	64.0
	Duration of employment	0.571	0.390	54.55	60.7	52.2	63.0
10 Years CVD Risk~	10 Years CVD Risk only	0.543	0.605	68.18	42.9	48.4	63.2
	ECG parameters	0.787	0.001*	77.27	75.0	70.8	80.8
	Copper zinc ratio	0.555	0.506	63.64	57.1	53.8	66.7
	Sodium Na^+	0.654	0.063	90.91	42.9	55.6	85.7
	MDA	0.605	0.207	40.91	85.7	69.2	64.9
	SOD	0.677	0.033*	86.36	42.9	54.3	80.0
	GST	0.555	0.506	45.45	85.7	71.4	66.7
	BMI	0.539	0.639	68.18	50.0	51.7	66.7
	WHR	0.544	0.598	63.64	50.0	50.0	63.6
	Duration of employment	0.558	0.482	59.09	50.0	48.1	60.9
Life time CVD risk~	Life time CVD risk only	0.548	0.564	4.60	100.0	100.0	57.1
	ECG parameters	0.786	0.001*	72.7	71.4	66.7	76.9
	Copper zinc ratio	0.555	0.506	63.6	57.1	53.8	66.7
	Sodium Na^+	0.654	0.063	90.9	42.9	55.6	85.7
	MDA	0.605	0.207	40.9	85.7	69.2	64.9
	SOD	0.677	0.033*	86.4	42.9	54.3	80.0
	GST	0.555	0.506	45.5	85.7	71.4	66.7
	BMI	0.573	0.379	54.6	60.7	52.2	63.0
	WHR	0.580	0.338	50.0	57.1	47.8	59.3
	Duration of employment	0.588	0.287	54.6	40.6	52.2	63.0

Figure 1. Performance of different biomarkers in predicting the optimal, lifetime, and the 10 years CVD risks among the enrolled divers

Predictors of lifetime and 10 years CVD risks among the studied divers and seafarers. In univariate analysis, history of smoking, disturbed levels of OSBMs (GH, GR, GPx, CAT and SOD), high plasma Cu+ and ECG changes reflecting LVH (S1/2+R5/6) were significantly associated with lifetime and 10 years CVD risk among the studied divers and seafarers. However, in our logistic regression model, history of smoking was the single predictor retained in the equation.

Likewise, none of the variables found associated with prolonged corrected QT interval, namely the WHR, BMI, duration of employment, history of smoking, disturbed levels of OSBMs (MDA, TAS, GSH, GR, CAT and SOD), varied trace metal levels (Fe+, Cu+ and Zn+) and some ECG changes (P-R interval, QRS complex, R-R SD and LVH (S1/2+R5/6)), appeared significant in our logistic regression model (Table 2).

Table 2

Predictors of lifetime CVD risk, 10 years CVD risk and prolonged corrected QT interval among the studied divers and marine seafarers

Parameter	Lifetime CVD risk				10 Years CVD Risk				Corrected QT Interval			
	Univariate analysis		#Multivariate analysis		Univariate analysis		#Multivariate analysis		Univariate analysis		#Multivariate analysis	
	(*n* = 100)		(*n* = 100)		(*n* = 100)		(*n* = 100)		(*n* = 100)		(*n* = 100)	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*
Duration of employment	1.023 (0.973–1.077)	0.373			1.061 (1.006–1.118)	0.030*	1.02 (0.95–1.10)	0.510	1.003 (0.954–1.056)	0.895		
Smoking	40.86 (10.92–152.85)	<0.001*	64.25 (13.73–300.2)	<0.001*	10.31 (4.08–26.07)	<0.001*	20.24 (5.31–77.17)	<0.001*	1.440 (0.640–3.241)	0.378		
Systolic blood pressure	1.015 (0.988–1.042)	0.284			1.031 (1.003–1.061)	0.032*	1.04 (0.99–1.07)	0.054	1.028 (0.999–1.058)	0.056		
Diastolic blood pressure	1.002 (0.962–1.043)	0.937			1.022 (0.981–1.065)	0.292			1.015 (0.974–1.059)	0.473		
Waist / height ratio	0.025 (0.000–9.156)	0.221			0.34 (0.001–106.25)	0.715			0.001 (0.000–0.747)	0.040*	0.03 (0.001–118.19)	0.405
BMI (kg/m^2)	0.922 (0.839–1.013)	0.09			0.969 (0.885–1.061)	0.494			0.904 (0.818–1.000)	0.049*		
Glucose (mg %)	0.980 (0.958–1.003)	0.084			0.989 (0.970–1.009)	0.279			0.988 (0.966–1.010)	0.292		
Triglycerides (mg/dl)	1.015 (0.998–1.032)	0.075			1.009 (0.994–1.025)	0.249			0.991 (0.975–1.007)	0.26		
Cholesterol (mg/dl)	1.019 (0.995–1.044)	0.123			1.018 (0.995–1.042)	0.122			0.997 (0.977–1.018)	0.804		
HDL (mg/dl)	1.025 (0.933–1.125)	0.609			0.956 (0.871–1.049)	0.341			1.030 (0.937–1.133)	0.537		
LDL (mg/dl)	1.016 (0.990–1.042)	0.233			1.022 (0.996–1.049)	0.105			0.998 (0.975–1.021)	0.849		
MDA (µl)	1.070 (0.985–1.163)	0.110			1.133 (1.039–1.235)	0.005*	0.94 (0.80–1.11)	0.490	1.189 (1.084–1.304)	<0.001*	1.11 (0.97–1.30)	0.127
TAS	0.554 (0.255–1.205)	0.136			0.591 (0.274–1.275)	0.180			0.295 (0.123–0.708)	0.006*	0.59 (0.16–2.16)	0.425
GST (µm/dl)	0.941 (0.815–1.086)	0.408			0.832 (0.714–0.970)	0.019*	0.88 (0.65–1.18)	0.400	0.775 (0.650–0.925)	0.005*	1.09 (0.81 –1.47)	0.566
GSH (U/ml)	0.915 (0.852–0.983)	0.015*	0.93 (0.78–1.10)	0.373	0.900 (0.837–0.968)	0.004*	0.99 (0.86–1.15)	0.931	0.829 (0.760–0.904)	<0.001*	0.87 (0.76–1.01)	0.061
GR	0.929 (0.880–0.980)	0.007*	0.97 (0.87–1.08)	0.532	0.907 (0.857–0.960)	0.001*	0.94 (0.84–1.05)	0.275	0.915 (0.864–0.970)	0.003*	1.08 (0.97–1.21)	0.183
GPx (U/ml)	0.010 (0.000–0.314)	0.009*	0.37 (0.001–178.6)	0.754	0.005 (0.000–0.178)	0.004*	0.15 (0.001–49.12)	0.518	0.037 (0.001–1.327)	0.071		
SOD (U/ml)	0.991 (0.984–0.997)	0.007*	1.01 (0.10–1.02)	0.163	0.989 (0.982–0.996)	0.002*	1.01 (0.99–1.03)	0.308	0.983 (0.974–0.991)	<0.001*	0.99 (0.98–1.01)	0.347
CAT	0.993 (0.989–0.998)	0.003*	0.99 (0.99–1.01)	0.427	0.992 (0.988–0.997)	0.001*	0.99 (0.99–1.01)	0.663	0.991 (0.986–0.996)	0.001*	0.99 (0.99–1.01)	0.589
Fe^+ (µm/dl)	1.006 (0.997–1.015)	0.193			1.009 (0.999–1.018)	0.071			1.019 (1.008–1.030)	0.001*	1.01 (0.99–1.03)	0.092
Cu^+ (µm/dl)	1.006 (1.001–1.010)	0. 010*	1.01 (0.997–1.01)	0.186	1.008 (1.004–1.013)	0.001*	1.01 (0.99–1.02)	0.067	1.007 (1.002–1.011)	0.002*	0.99 (0.99–1.00)	0.212
Zn^+ (µm/dl)	0.996 (0.982–1.010)	0.566			0.991 (0.977–1.004)	0.183			0.981 (0.966–0.996)	0.014*	0.99 (0.97–1.02)	0.691
Ca^+ (mmol/l)	1.015 (0.504–2.042)	0.968			1.180 (0.591–2.358)	0.639			1.348 (0.658–2.762)	0.415		

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End of the Table 2

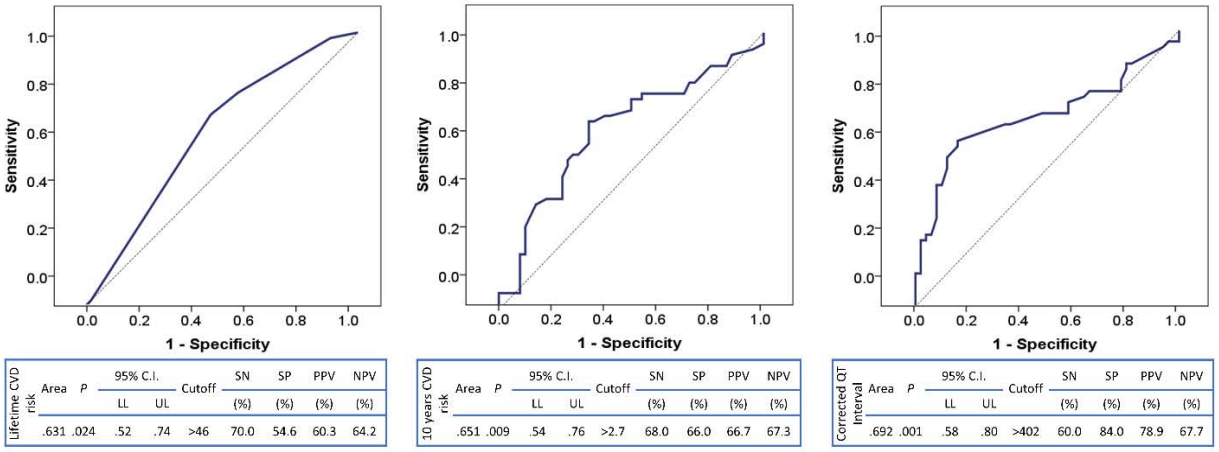
Parameter	Lifetime CVD risk				10 Years CVD Risk				Corrected QT Interval			
	Univariate analysis		#Multivariate analysis		Univariate analysis		#Multivariate analysis		Univariate analysis		#Multivariate analysis	
	(*n* = 100)		(*n* = 100)		(*n* = 100)		(*n* = 100)		(*n* = 100)		(*n* = 100)	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*
K^+ (mmol/l)	1.396 (0.464–4.200)	0.553			0.876 (0.296–2.596)	0.812			0.955 (0.313–2.921)	0.936		
Na^+(mmol/l)	1.004 (0.905–1.115)	0.933			1.017 (0.917–1.127)	0.752			0.946 (0.850–1.054)	0.316		
Na^+/K^+ ratio	0.958 (0.841–1.092)	0.524			1.017 (0.894–1.157)	0.798			0.987 (0.864–1.127)	0.846		
Urea (mg/dl)	0.956 (0.876–1.044)	0.317			0.964 (0.884–1.051)	0.405			0.973 (0.889–1.064)	0.546		
Creatinine (mg/dl)	0.136 (0.004–4.671)	0.269			0.618 (0.019–19.715)	0.785			0.586 (0.016–20.97)	0.770		
Uric acid (mg/dl)	1.366 (0.888–2.103)	0.156			1.280 (0.842–1.946)	0.249			1.105 (0.724–1.688)	0.644		
AST (mg/dl)	0.975 (0.922–1.032)	0.385			0.960 (0.908–1.016)	0.155			1.013 (0.957–1.072)	0.661		
ALT (mg/dl)	0.970 (0.919–1.024)	0.274			0.948 (0.896–1.004)	0.069			1.027 (0.973–1.085)	0.335		
Bilirubin (mg/dl)	0.113 (0.004–2.849)	0.186			0.214 (0.009–5.089)	0.340			0.129 (0.005–3.603)	0.228		
Rhythm	1.049 (0.399–2.759)	0.922			1.120 (0.426–2.942)	0.819						
Rate/min	0.994 (0.969–1.019)	0.613			0.994 (0.970–1.018)	0.624			0.995 (0.971–1.020)	0.703		
Axis	1.203 (0.631–2.292)	0.575			1.640 (0.843–3.192)	0.145			1.411 (0.756–2.633)	0.280		
P wave	1.470 (0.810–2.667)	0.205			1.281 (0.733–2.236)	0.384			1.487 (0.854–2.590)	0.161		
P-R interval (msec)	1.006 (0.992–1.021)	0.392			1.011 (0.997–1.026)	0.121			1.018 (1.003–1.033)	0.019*	1.00 (0.98–1.02)	0.824
QRS complex (msec)	1.008 (0.988–1.029)	0.433			1.012 (0.992–1.033)	0.230			1.023 (1.001–1.044)	0.037*	1.01 (0.98–1.05)	0.425
QT WAVE (msec)	1.005 (0.993–1.018)	0.405			1.001 (0.989–1.013)	0.894			0.995 (0.982–1.007)	0.408		
Corrected. QT interval	1.005 (0.992–1.017)	0.442			1.002 (0.990–1.014)	0.741						
$S_{1/2}+R_{5/6}$ (mV) (msec)	1.062 (1.001–1.127)	0.047*			1.076 (1.014–1.142)	0.015*	0.98 (0.89–1.09)	0.727	1.100 (1.034–1.170)	0.002*	1.00 (0.91–1.10)	0.988
R-R MIN (mm)	1.093 (0.954–1.251)	0.201			1.078 (0.944–1.231)	0.266			1.066 (0.931–1.219)	0.356		
R-R MAX (mm)	1.092 (0.971–1.229)	0.141			1.097 (0.977–1.232)	0.118			1.122 (0.995–1.265)	0.061		
R-R mean (mm)	1.097 (0.965–1.248)	0.157			1.093 (0.964–1.241)	0.166			1.102 (0.968–1.255)	0.142		
R-R SD (msec)	1.193 (0.662–2.150)	0.557			1.448 (0.800–2.623)	0.222			2.222 (1.163–4.248)	0.016*	1.63 (0.69–3.87)	0.264
ECG	1.930 (0.773–4.816)	0.159			2.316 (0.944–5.679)	0.067			2.236 (0.926–5.400)	0.074		

Note: CAT – catalase; CI – confidence interval; GR – glutathione reductase; GSH – reduced glutathione; GST – glutathione transferase; GPx – glutathione peroxidase; MDA – malonic dialdehyde; OR – odds ratio; SOD – superoxide dismutase; TAS – total antioxidant status. All variables with $p < 0.05$ was included in the multivariate; * – Statistically significant at $p \leq 0.05$.

Performance of the lifetime CVDR, 10 Years CVDR and corrected QT interval risk prediction models in predicting CVD risk. Cutoff points greater than 46, 2.7, and 402 with the best trade-off between sensitivity and specificity significantly defined lifetime CVD risk, the 10 years CVD risk and the corrected QT interval among the study population (AUC (95 % CI) = 0.631 (0.521–0.740), 0.651 (0.542–0.761), and 0.692 (0.584–0.800) respectively, $p < 0.05$). The positive predictive value (PPV) and negative predictive value (NPV) of the chosen cutoff point were 60.3, 66.7, 78.9 and 64.3, 67.3, 67.7, respectively (Figure 2).

Risk stratification of the studied divers and seafarers according to the proposed risk prediction models. According to the preset cutoff points, 70.0 % of diver were at high risk of having lifetime CVD compared to 46.0 % of the marine seafarers ($p = 0.015$). Similarly, 68.0 % and 60.0 % of diver were at high risk of having 10 years CVD risk and prolonged corrected QT interval compared to 43.0 % and 16.0 % of the controls respectively ($p < 0.001$) (Table 3).

Basically, CVR prediction models are important in CVDs prevention and management. It is critical to find such biomarkers that indicate the presence of preclinical



	Area	P	95% C.I. LL	95% C.I. UL	Cutoff	SN (%)	SP (%)	PPV (%)	NPV (%)
Lifetime CVD risk	.631	.024	.52	.74	>46	70.0	54.6	60.3	64.2
10 years CVD risk	.651	.009	.54	.76	>2.7	68.0	66.0	66.7	67.3
Corrected QT Interval	.692	.001	.58	.80	>402	60.0	84.0	78.9	67.7

Figure 2. Performance of different risk prediction models in predicting CVD risk

Table 3

Risk stratification of the studied divers and seafarers according to the proposed risk prediction models

Parameter	Divers ($n = 50$)		Marine seafarers ($n = 50$)		Comparison test (χ^2)	Validity of differences (p)
	abs.	%	abs.	%		
Lifetime CVD risk						
No risk (≤ 46)	15	30.0	27	54.0	5.911	0.015*
Positive risk (> 46)	35	70.0	23	46.0		
10 years CVD risk						
No risk (≤ 2.7)	16	32.0	33	66.0	11.565	< 0.001*
Positive risk (>2.7)	34	68.0	17	34.0		
Corrected QT interval						
No risk (≤ 402) (milliseconds)	20	40.0	42	84.0	20.543	< 0.001*

Note: χ^2 – Chi-square test. All variables with $p < 0.05$ were included in the multivariate; p – p value for comparing between the studied groups; * – statistically significant at $p \leq 0.05$.

disease in individual subjects like blood biomarkers of atherosclerosis. The ASCVDR score estimator is used in clinical practice to determine the vascular element of the CVR [17–19]. However, clustering of biomarkers as "multi-markers" increases sensitivity and, consequently, stratification of CVR assessments. In this regard, novel biomarkers include OSBMs, ECG, and trace metals.

The present comparative cross-sectional study was conducted to assess the CVR in professional divers using the ASCVD estimator and some novel biomarkers including electrophysiological changes in the ECG, some OSBMs and some trace metals [12, 20, 21].

Consistent with previous reports, high BMI was prevailing among divers [22, 23] and correlated with an increase in the 10 years and lifetime risks of CVD[3] [18, 24]. The mean WHtR was significantly lower in divers than in controls and correlated with prolonged corrected QT interval, which reflects disturbance in the electrophysiological status. This is agreed with the previous studies that reported WHtR as a predictor of CVD risk [17, 18, 25–27].

The main aim in the present study was to assess the CVR in professional divers by using the ASCVD estimator. The mean lifetime, 10 years and optimal CVD risks were significantly higher in divers than in marine seafarers. Moreover, the optimal CVD risk in divers was greater than that of the general population (74.0 % vs 34.0 %, respectively) in the 10 years CVR. The study [10] showed that the prevalence of some cardiovascular symptoms and diseases might be higher in male former divers than in the general population and that diving might have adverse long-term cardiovascular effects. For the marine seafarers, it was 66.89 % more than the optimal CVD for the 10 years risk. So, compared with divers it is still less by 7.12 %. Oldenburg and co-workers showed that German seafarers are twice to three times at more risk for 10 years CVD risk [28, 29], although in the present study, seafarers were at lower CVR. This may be attributed to the age difference between this our study controls as opposed to the German seafarers.

Electrophysiological changes revealed by ECG were obvious among our diver cohort. Indeed, electrophysiological changes are more common and important clues as they are more liable to aggravate arrhythmias in divers. Adding electrophysiological changes to the CVR assessment will help also in risk stratification. Electrophysiological changes precipitating arrhythmias are more relevant etiological factor for cardiac related deaths rather than ischemic coronary vascular changes [30–33]. It is worth noting that electrophysiological changes seen in ECG are the strongest predictive parameter in the study of the CVR. It showed significant difference than other tested parameters in the ROC curve analysis of the optimal, 10 years and lifetime CVD risk. There were no other studies, which described corrected QT wave except a single recent study[4]. The authors reported significant change in the pulse rate, corrected QT, and T wave before and after diving but did not mention any cutoff point.

[3] Lamon-Fava S., Wilson P.W., Schaefer E.J. Impact of body mass index on coronary heart disease risk factors in men and women: the Framingham Offspring Study. *Arterioscler. Thromb. Vasc. Biol.*, 1996, vol. 16, no. 12, pp. 1509–1515. DOI: 10.1161/01.atv.16.12.1509

[4] Salah H., El-Gazzar R.M., Abd El-Wahab E.W., Charl F. Oxidative and cardiovascular stress among professional divers in Egypt. *medRxiv: the preprint server for health sciences.* Available at: https://www.medrxiv.org/content/10.1101/2022.10.20.22281338v1.article-metrics (December 07, 2024).

The role of race metals and OS in the pathogenesis of CVDs is well established [21, 34, 35]. Oxidative stress is linked to increased levels of Cu^+ and decreased levels of Fe^+ and Zn^+ [35–37]. Also, blood Ca^+ level may increase arterial wall stiffness and subsequently the 10 years CVD risk as assessed by the Framingham score [38]. This is in line with the present work, where the evidence for disturbed electrolytes and trace metal levels as well as increased OS was found in our examined divers as manifested by abnormal levels of OSBMs. In the present study, on univariate analysis, lower levels of Na^+ and higher level of Cu^+ and Ca^+ were significantly associated with CVR although they did not appear in the logistic regression model. This could be attributed to the small sample size and large number of variables used in the analysis. Few researches mentioned the effect of diving on the trace metals, especially the saturation deep diving, which affects the hemoglobin iron level[5].

ROC curve analysis was done in this study to detect the sensitivity of the studied biomarkers in CVRA compared to the ASCVDR estimator as an established and approved tool. The greater the AUC is the more sensitive and specific the test parameter will be. The analysis was run for the optimal CVD risk, 10 years CVD risk and the whole lifetime risk. The best performance was noticed for ECG changes. Indeed, ECG changes are of utmost importance they are the most specific parameter related to the CVD risk. This comes in agreement with a study done by Tocci et al. (2017), which demonstrated for the first time that other biomarkers could be added independently to global risk estimators for CVD risk assessment [39]. Furthermore, our findings support the postulation that adding biomarkers could allow better individual CVR detection. The ECG changes were also found to be a more specific biomarker as the OS changes could occur in other physiological and pathological conditions. ECG changes as a biomarker are characterized by large availability, simple interpretation, and cost-effectiveness and should therefore be preferred in the CVD risk assessment [12].

In the present study, smoking, duration of employment, OSBMs, some trace metals, ECG change denoting left ventricular hypertrophy ($S_{1,2}$+$R_{5,6}$) were significantly associated with CVR in both divers and seafarers. Nevertheless, smoking was the single predictor of CVR in multivariate logistic regression analysis, probably because other variables in the model were affecting the CVR through a cross-interacting manner. Collectively, OSBMs and trace metals need further research to predict their effects with larger sample sizes.

The proposed lifetime CVR, 10 years CVR and the corrected QT wave interval prediction models showed better sensitivity and specificity in predicting CVR when compared to the ASCVDR estimator. Lifetime and 10 years CVR scores of 46 and 2.7 respectively were significant in estimating CVR. Above these points, divers are considered at higher CVD risk. Likewise, a corrected QT wave interval score of 402 msec was significant in estimating CVR. Above this point, divers are considered at higher CVD risk. This was in agreement with a study investigated the arrhythmia factors in scuba divers and

[5] Nakabayashi K., Mizukami H., Hashimoto A., Oiwa H. Change in red blood cell production rate during a 330 msw saturation dive simulation. *Undersea Biomed. Res.*, 1991, vol. 18, suppl., pp. 32.

concluded that QT prolongation can be recorded in divers after diving. Prolongation of the QT wave increases the CVR of arrhythmia [31]. In addition, the risk stratification of divers and seafarers that was based on the total scores of the proposed lifetime CVR, 10 years CVR and the corrected QT wave interval prediction models and their preset cutoff points showed statistically significant differences between the two groups. This suggests that the performance of the proposed indices is comparable to the ASCVDR estimator in predicting the CVDR. Thus, the ASCVDR estimator could assess the vascular CVR factors, while the electrophysiological factors could be determined by the corrected QT interval.

Conclusion and recommendations. Professional divers are at higher risk of cardiovascular diseases as measured by ASCVD estimator in term of increased 10 years risk score as well as life time compared to the same levels reported among the control group. Cardiovascular risk assessment of professional divers is thus recommended in the periodic medical examinations and during fitness examinations. During the periodic examination of the divers and seafarers for fitness the following should be emphasized: 1) careful monitoring of systolic blood pressure; 2) use of the ASCVD estimator for assessing CV risk. Analysis of the results should be done considering cutoff points of ≤ 46 and ≤ 2.6 for the life time and 10 years risk detection respectively; 3) calculation of the corrected QT wave interval in the resting ECG with a cutoff point of ≤ 402 milliseconds should be considered for further assessment and investigation by specialized cardiologist for diving fitness. Although highly predictive, oxidative stress biomarkers such as SOD and trace metals levels (Cu^+/Zn^+) should not be done as routine unless their role in CVR assessment is reproduced and validated in further research on larger sample sizes.

Preventive measures for CVR factors and promoting better quality of life should be advised for professional divers and seafarers by emphasizing and not limited to: 1) tight smoking prevention and control programs, 2) nutritional health education encouraging consumption of antioxidants and Zn supplements, 3) health education for prevention and control of cardiovascular diseases.

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