Blood biomarkers for assessing headaches in healthcare workers after wearing biological personal protective equipment in a COVID-19 field-hospital

Francisco Martín-Rodríguez
Raquel M. Portillo Rubiales
Laura N. Fadrique Millán
Virginia Carbajosa Rodríguez
Ancor Sanz-García (ancor.sanz@gmail.com)
Gabino Mozo Herrera
Guillermo J. Ortega
Esther Durá Ballester
Miguel Ángel Castro Villamor
Raúl López Izquierdo

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Abstract

The consequences of wearing biosafety equipment by healthcare professionals during their work and the prediction of such consequences need to be assessed. To analyze the role played by different blood biomarkers in predicting the appearance of headaches in healthcare workers wearing personal protective equipment (PPE) in a COVID-19 treatment unit, a Prospective cohort study of 38 healthcare workers from a convalescence unit of patients with COVID-19 in a field hospital was performed during April 2020. Blood analysis was carried out before the start of the 4 hours shift of the volunteers equipped with PPE. After decontamination, there were asked if they had suffered from headache, obtaining the binary outcome. This study included 38 participants with a median age of 29 years (25th-75th percentile: 26-44 years old), 73.7% female (28 cases). 44.7% (17 cases) had a headache after wearing PPE for 4 hours. The baseline creatinine value reflected a specific odds ratio in the regression model of 241.36 (95% CI: 2.50-23,295.43; p=0.019), and an AUC of 0.737 (95%CI: 0.57-0.90; p<0.01). Blood creatinine is a good candidate for predicting the appearance of a *de novo* headache in healthcare workers after wearing PPE for 4 hours in a COVID – 19 unit.

Introduction

The outbreak of *coronavirus disease 2019* (COVID-19) caused by the SARS - CoV- 2 at the end of December 2019 force the World Health Organization to declare a global public health emergency which, due to its rapid worldwide escalation, has reached the category of pandemic (1).

Since the start of this new infection, healthcare workers have been identified as one of the groups most affected by this disease. On February 11, the Chinese Center for Disease Control and Prevention announced an infection rate among healthcare workers of 3.8% (1716 cases) (2), a figure which has been increasing since then up to levels of 20% in Italy (3) for instance, raising major concerns in the worldwide public institutions (4). Since the beginning of the pandemic, this data highlights the importance of wearing a personal protective equipment (PPE) as one of the mainstays for the protection of professionals and to prevent the spread of the virion (5).

Healthcare systems must ensure the safety of their professionals by providing them with utmost level of biosafety possible (6) (7). The correct use of PPEs among healthcare workers has effectively demonstrated reduction of infections in several health emergencies (8), but at the expense of causing collateral effects such as a decrease in the field of vision, hearing alterations, increased feeling of warmth, reduced mobility, difficulty in breathing properly, etc. (9). Also, the appearance of physiological consequences such as dizziness, nausea, vomiting, headaches, hypoglycemic episodes (10), and even psychological manifestations such as anxiety, stress, bradypsychia, etc. (11), have been described.

COVID-19 treatment units are complex settings, in many cases unfamiliar to the worker, where they must perform precise and technical procedures using fine motor skills while wearing PPEs (12) (13). If we add to these special working conditions the fact that a headache may occur, working conditions become

significantly more complicated directly affecting the thinking capacity, the decision-making process, and the outcome of the actions carried out, with the consequently risk for both the patient and the worker (14).

The use of prognosis biomarkers is a reality in the current clinical practice and headache is not an exception, where several biomarkers have been studied such as neuropeptides, cytokines, adipokines, etc. (15). These types of biomarker are very specific and difficult to process without the appropriate equipment and specialized laboratory staff, so their rapid bedside use is not currently recommended. The development of small-scale and reliable point-of-care testing (POCT) has allowed for analyses in multiple clinical contexts (16).

This main objective of this study was to analyze the role played by different blood biomarkers –sodium, chlorine, calcium, potassium, creatinine, blood urea nitrogen, urea, lactate, and glucose- to predict the appearance of headaches during/after wearing PPEs in healthcare workers in a COVID-19 treatment unit.

Methods

Study Design and Setting

A preliminary prospective study was carried out in a cohort of volunteer healthcare workers taken from a convalescence unit for patients with COVID-19 at the Valladolid COVVA field hospital, between April 18 and 22. The COVVA field hospital has 200 beds and was designed as a unit for patients with confirmed infection and initially good clinical progress. The facility was constructed in a 3,800 m2 space with the highest biosafety standards. The field hospital has electronic admission, medical history service, radiology, basic ultrasound, laboratory, pharmacy, an ambulance, etc., and a hospitalization capacity of 200 patients.

The Research Ethics Committee of Rio Hortega University Hospital approved the study protocol (PI-075/20). All participants signed informed consent. This study was in accordance with Good Clinical Practice and the Declaration of Helsinki. The review protocol of this study was registered with ICTRP (doi.org/10.1186/ISRCTN18348009). This study is reported in line with the STROBE statement (17) and it is registered as trial: ISRCTN18348009 https://doi.org/10.1186/ISRCTN18348009

Participants

Participants in the study were volunteers between 18 and 65 years old, physicians, nurses or medical assistants, all working in the field hospital. Thirty-eight subjects were selected at random from an opportunity sample of 95 volunteers to accomplish the maximum number of samples that the current situation allowed us to analyze.

The exclusion criteria involved not signing the informed consent and/or having a headache or a temperature above 37.5 ºC at the time of the study. Volunteers with any of the following conditions were not eligible: body mass index greater than 40 kg/m2, major surgery in the last 30 days, taking anticoagulants or anticonvulsants and/or systemic cutaneous or acute pulmonary diseases. Additionally,

all the professionals must follow the working rules on the COVID – 19 zone of the field hospital, which included a correct hydration (500ml of water or isotonic drink) before entering into the COVID – 19 area.

Study Protocol and Measures

After signing the informed consent, the volunteers underwent a blood test 15 minutes before starting their working day.

All the samples were taken from the veins of the right antecubital fossa by the same registered nurse. The blood analysis was carried out using the epoc® Blood Analysis System (Siemens Healthcare GmbH, Erlangen Germany). The following biomarkers were collected: sodium, chlorine, calcium, potassium, creatinine, blood urea nitrogen, urea, lactate and glucose.

After the analysis, under the supervision of a biohazard specialist and in accordance with the standards of the European Center for Disease Prevention and Control, the professionals were equipped with a category-III PPE, type 4B/5B/6B (18). The standard biological PPE was composed of a protective coverall, disposable gloves, nitrile non-powdered, panoramic glasses, and a transparent face-shield. In addition, the volunteers were randomly equipped with a face mask 2 [filtering facepiece (FFP)] Aura™ (3M, Minnesota, USA) or N95 face mask (3M, Minnesota, USA).

Once equipped with PPEs, the professionals worked for a period of four hours. At the end, and after passing through a decontamination tunnel, a biohazard specialist helps the professional to take off the PPE in a scheduled manner. In a clean room after decontamination, a registered nurse asked them if they had or have a headache. They were specifically asked about the nature of the headache, excluding any mechanical pain caused by the panoramic glasses, face shield or face masks.

Outcome and Data Abstraction

The principal result variable was the presence of a headache after four hours of continuous working with the PPE.

For all those subjects that met the inclusion criteria and entered into the working area during the study time period, the following variables were obtained: sex, age, professional category, years of experience, time wearing the PPE, blood test-derived data, and the presence or not of a headache.

All staff were aware of the objectives of the study and received specific information about the operation, cleaning, maintenance, and calibration of the analysis equipment. Each analysis was performed with a self-calibrating card with control of expiration dates, serial numbers, and batch numbers.

The data of all the participants was recorded electronically in a database created for this purpose. The analytical data was transferred via Bluetooth from the epoc® Blood Analysis System to the principal investigator's computer. To establish an accurate data link, the card's serial number, age, sex, and time of analysis were linked to each test card.

Missing data

Using logical, range, and consistency tests, a database was refined, which resulted in a total of 16 variables. A full variable-by-variable analysis of unknown data was then performed, leaving only full data sets for the analysis. The study variables did not present missing data. The case registration form was checked to eliminate ambiguous elements to guarantee the robustness of the data collection instrument.

Data Analyses

Normality tests were performed on all the quantitative variables (Shapiro-Wilk and Lilliefors tests) observing that sodium, calcium, potassium, creatinine, and lactate reflect normal distribution with the other variables reflecting non-normal distributions; therefore, all the quantitative variables were described as median and interquartile range (25th-75th percentile). The qualitative variables were described using absolute frequencies with their confidence interval of 95% (CI95%).

The Mann-Whitney U test was used to compare quantitative variable measurements. The chi-squared test was used for 2x2 contingency tables and/or proportional contrast to stipulate the association or dependency relationship between qualitative variables. If necessary (percentage of cells with expected values less than five, greater than 20%), Fisher's exact test was used.

A logistic regression was used to determine the optimal model for the outcome (headache) prediction. An Akaike information criteria algorithm was used with backward elimination and forward selection of variables providing a final model. The discrimination capacity of the final model and the different biomarkers that presented a significant p-value ($p<0.05$) was assessed using the area under the curve (AUC) of the receiver operational characteristics (ROC), calculating, in each case, the p-value of the hypothesis testing (H_0: ABC=0.5). The results of the ROC show a CI of 95% after 300 resamples, as well as the best score that offered joint greater sensitivity and specificity in each case, also calculating the positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio for these scores.

Also, the analysis of variance (ANOVA) of two factors was used to determine the possible interaction and principal effect of each factor for those appearing significant in the logistic regression model.

The statistical analysis was conducted using IBM SPSS Statistics for Apple version 20.0. (IBM Corp, Armonk USA) and own codes and base functions in R, version 3.5.1 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

Results

Of a total of 95 volunteers that agreed to participate in the study, 46 participants were chosen at random and were then randomized based on the type of face mask to be worn during their work (N95 or FFP2). After exclusions, the final number of participants analyzed was 38 (eFigure 1 of supplementary data). The median age was 29 years old (25th-75th percentile: 26-44 years) and 73.7% (28 cases) were female.

Nurses contributed most (15 workers, 39.5%) followed by physicians (12 workers, 31.6%) and medical assistants (11 workers, 28.9%), with a median of 4 years (25th-75th percentile: 3-8 years) of professional experience. The median time working with the PPE was 4 hrs 10 min (25th-75th percentile: 4 h 1 min - 4 h 24 min). 44.7% (17 cases) had a headache after wearing PPE for 4 hours. Table 1 reflects the demographic characteristics and the analytical data of the two groups analyzed.

Table 1. Characteristics of the study population

Characteristic[1]	Total n=38	Headache			
		No n=21	Yes n=17	Odds ratio (95%CI)	*p*-value
Age (years)	29 (26-44)	29 (26-42)	30 (27-45)	1.01 (0.95-1.07)	0.674[2]
Sex (female)	28 (73.7)	18 (85.7)	10 58.8)	4.20 (0.88-19.94)	0.071[3]
Employment					
Physician	12 (31.6)	6 (28.6)	6 (35.3)		
Nurse	15 (39.5)	8 (38.1)	7 (41.2)	1.75 (0.32-9.29)	0.511[3]
M. assistant	11 (28.9)	7 (33.3)	4 (23.5)	1.53 (0.31-7.53)	0.600[3]
Exp. (years)	4 (3-8)	4 (1-5)	4 (3-10)	1.04 (0.95-1.13)	0.352[2]
Mask type					
N95	19 (50.0)	7 (33.3)	12 (70.6)		
FFP2	19 (50.0)	14 (66.7)	5 (29.4)	4.80 (1.20-19.12)	**0.026**[3]
PPE time (hours)	4:10 (4:01-4:25)	4:10 (4:03 AM-4:25)	4:05 AM (3:58 AM-4:21)	1.00 (0.99-1.00)	0.640[2]
Blood test					
Na+ (mEq/l)	141 (140-143)	141 (140-142)	142 (140-143)	1.12 (0.77-1.62)	0.530[2]
K+ (mEq/l)	3.9 (3.6-4.0)	4.0 (3.8-4.0)	3.8 (3.5-4.0)	0.26 (0.02-2.63)	0.257[2]
Ca++ (mEq/l)	1.27 (1.23-1.29)	1.27 (1.25-1.29)	1.25 (1.23-1.29)	NA	0.495[2]
Cl- (mEq/l)	104 (103-105)	104 (103-105)	104 (103-105)	1.08 (0.71-1.66)	0.701[2]
Urea (mg/dl)	5.1 (4.4-5.7)	5.1 (4.5-5.5)	5.0 (4.2-6.5)	1.38 (0.79-2.41)	0.252[2]
Crea (mg/dl)	0.91 (0.76-1.03)	0.83 (0.72-0.96)	0.99 (0.87-1.11)	241.36 (2.50-23,295.43)	**0.019**[2]
BUN (mg/dl)	12 (10-13)	12 (10-13)	13 (10-15)	1.11 (0.91-1.36)	0.287[2]
Glu (mg/dl)	96 (90-103)	96 (88-103)	96 (91-106)	1.00 (0.96-1.04)	0.936[2]
Lac (mmol/l)	1.13 (0.81-1.53)	1.13 (0.83-1.47)	1.14 (0.79-1.53)	1.07 (0.27-4.20)	0.914[2]

[1]Values expressed as total number (fraction) and medians [25th percentile-75th percentile] as appropriate. [2]The p-values were calculated with the Mann-Whitney U-test. [3]The p-values were calculated with the chi-square test. OR: odds ratio; CI: confidence interval; M: medical: Exp: experience; FFP: filtering facepiece; PPE: personal protection equipment; Na+: sodium; K+: potassium; Ca++: calcium; Cl-: chlorine; Crea: creatinine; BUN: blood urea nitrogen; Glu: glucose; Lac: lactate

The final model derived from the logistic regression selected only the variables face mask and creatinine to predict headaches (Table 2). This model presented and AUC 0.777 (95%CI: 0.57-0.90; p<0.01).

Table 2. Predictive model for headaches

	B(SE)	p-value	OR	IC95% for OR	
				Lower	Upper
Face mask	-1.33(0.75)	0.077	0.26	0,07	0,89
Creatinine	5.003(2.43)	0.04	148.8	3.71	12584
Constant	-2.76 (2.5115)	0.27	0.06		

B(SE): Estimate (standard error); OR: Odd ratio; IC95%: 95% confidence interval.

Similarly, in the univariate analysis, creatinine and face masks were the only significant variables, as shown in Table 1. In terms of creatinine levels, it can be seen that subjects with headaches presented higher levels of it (Figure 1). We further analyzed the potential interaction and principal effects of creatinine and face mask on headache. To do that, a two-factor ANOVA -mask type and creatinine- was performed, which did not show significant interaction between both variables and only a significant effect was found for creatinine (eTable1 of supplementary data). This is in line with the logistic regression model, which selected face mask but did not present a significant effect for this variable. Therefore, only creatinine was considered for subsequent analyzes. The baseline creatinine value presented a specific odds ratio in the regression model of 241.36 (95% CI: 2.50-23,295.43), with a *p*-value of 0.019, indicating that the higher the level of creatinine, the greater the risk of headaches.

To determine the validity of creatinine in predicting headaches, the AUC was calculated obtaining a value of 0.737 (95%CI: 0.57-0.90; p<0.01) (Figure 2). In addition, the AUC was calculated to analyze the predictive power of creatinine based on the type of mask worn, obtaining a value of 0.702 (95%CI: 0.46-0.94; p=0.098) for the N95 face mask and 0.764 (95%CI: 0.49-1.00; p=0.055) for the FFP2 face mask.

Table 3 shows further characteristics derived from the ROC curve for creatinine and for the type of mask worn, both cases associated with the ability to predict headaches. In the case of creatinine, the cut-off point stands at 0.87 mg/dl, as can be seen in Figure 1, with five subjects below this level in the group affected by headaches. In addition, creatinine proves to have a high predictive value, as can be seen from the sensitivity and specificity reported in the table. However, the results observed by type of face mask are consistent with the results obtained and their lack of statistical significance in the ANOVA of two factors (eTable1 of supplementary data).

Table 3. Measures of the predictive model for creatinine and headaches

	Global	Mask type	
		N95	FFP2
Headache prevalence	44.7	63.2	26.3
Creatinine cut-off point (mg/dl)	0.87	1.10	0.87
Area under the curve	0.737 (0.57-0.90)	0.702 (0.46-0.94)	0.764 (0.49-1.00)
p-value	<0.01	0.098	0.055
Sensitivity	88.2 (65.7-96.7)	41.7 (19.3-68.0)	100 (56.6-100)
Specificity	61.9 (40.9-79.2)	100 (64.6-100)	64.3 (38.8-83.7)
Positive predictive value	65.2 (44.9-81.2)	100 (56.6-100)	50.0 (23.7-76.3)
Negative predictive value	86.7 (62.1-96.3)	50.0 (26.8-73.2)	100 (70.1-100)
Likelihood ratio (+)	2.32 (1.31-4.10)	0	2.80 (1.39-5.65)
Likelihood ratio (-)	0.19 (0.05-0.73)	0.58 (0.36-0.94)	0
Diagnostic accuracy	73.7 (58.0-86.0)	63.2 (41.0-80.9)	73.7 (51.2-88.2)
Pretest probability	44.7	63.2	26.3
Youden's test	0.5	0.4	0.6

*Bracketed numbers indicate 95% confidence interval; FFP: filtering facepiece

Discussion

The results presented here show that creatinine values, taken from a blood test, can predict whether frontline health workers in a field hospital during the current COVID-19 pandemic will develop headaches while working with PPEs. These results are in line with previous findings in which headaches and neck pain are largely associated with the use of PPEs on different working environments (10) (19) (20). In particular, it is already know that protective masks, in particular the N95, affects workers performance and contribute to the onset of a headache (21) (22) (23).

Although both types of face mask provide the same protection against biohazards (24) (25), some differences between them were found in our study. Amongst the subjects who developed a headache, two-thirds of them have used N95 masks. This is readily understood taking into account that FFP2 masks have an exhalation valve that may protect from the development of headaches (26).

Blood tests analysis revealed that only creatinine values before working in the COVID-19 zone provide a robust biomarker to predict the appearance of headaches at the end of the work. Various studies, such as those by Gozubatik-Celik G *et al* (27), in patients during dialysis, or by Poyrazoğlu HG *et al* (28) in an infant population, have already described this correlation between creatinine and the appearance of headaches. It should be noted that the assessment of creatinine levels using POCT is a reliable and fast method and it is performed with a simple venous analysis or capillary blood sample (29) (30). In this sense, dehydration has been related to a headache increase (31) and also to creatinine levels increase (32). However, this is not the case in our subjects since the blood sample was taken before their stay on the COVID-19 zone and their hydration was previously ensured from the shift start. As with dehydration, changes in blood volume could affect the present results; this was solved by ensuring a systolic blood pressure below 150 mmHg and above 80 mmHg before entering into the COVID-19 zone.

Our study has several limitations, however. The first one is the sample size. Restrictions due to the current pandemic make difficult accessing larger cohorts, even more in units exclusively devoted to the care of COVID-19 patients where biosafety is vital. In order to generalize the results presented here, a multicenter study should be conducted in the future. A second issue involves the possible bias in the participant selection. The sample was taken from among all workers at the COVVA hospital. To minimize this bias, participants were selected with no stratification for sex, age or professional category, and all volunteers were randomized to find out who would form part of the next phase of the study. There was no consideration of whether professionals had suffered from any type of chronic headache prior to the study. Confounding factors that could modify creatinine levels, such as the effect of certain medications (except for anticonvulsants and anticoagulants) or eating large amount of meat were not considered. Finally, the analytical procedure may be affected by the inter-personal factor. To avoid this bias as much as possible, all staff involved in the study received a procedure manual and initial training on how to collect data, and measurement and analytical instruments.

Conclusions

Data presented here show a high incidence of *de novo* headaches in healthcare workers after four hours of continuous use of PPEs. Prediction of who will develop headaches certainly is an issue of major concern for the healthcare system. According to our results, the use of blood creatinine as a putative biomarker could help in predicting the appearance of a *de novo* headache in healthcare workers after wearing PPEs for 4 hours in a COVID – 19 unit. Healthcare management should consider an early assessment of susceptibility to masks by enforcing blood tests before exposing the personnel to biohazard scenarios.

Declarations

Conflict of Interest Statement:

No conflict.

All signing authors fulfill the requirements of authorship and have declared the non-existence of potential conflicts of interest. The authors have no disclosures to make. On behalf of the other authors, the corresponding author guarantees the accuracy, transparency and truthfulness of the data and information contained in the study, that no relevant information has been omitted, and that all discrepancies between authors have been adequately resolved and described.

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Author Contributions:

Concept and design: Martín-Rodríguez, López Izquierdo.

Acquisition, analysis, or interpretation of data: all authors.

Drafting of the manuscript: Martín-Rodríguez, López Izquierdo, Sanz-García, Ortega.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Martín-Rodríguez, Sanz-García, Ortega.

Administrative, technical, or material support: Portillo Rubiales, Fadrique Millán, Carbajosa Rodríguez, Mozo Herrera.

Supervision: Martín-Rodríguez.

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Figures

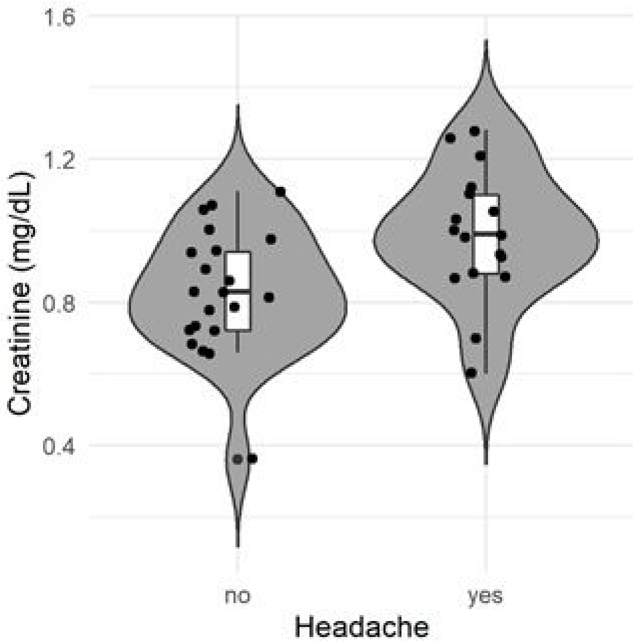

Figure 1

Distribution of creatinine levels according to the presence of a headache. The plot shows the distribution (gray shaded area), the boxplot and value of each patient (dots) of creatinine levels for both groups (absence or presence of headache).

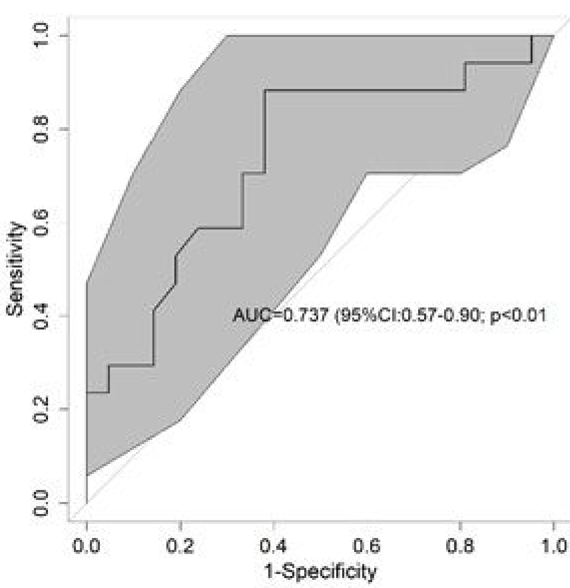

Figure 2

Receiver operational characteristic of creatinine for headaches. The bold line shows the value of the COR curve and the gray shading is the result of 300 resamples. In the center of the graph is the area under the curve (AUC) and its 95% confidence interval and the p-value of the comparison against the null hypothesis (AUC=0.5). ROC: Receiver operational characteristic; AUC: Area under the curve

Supplementary Files

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- Supplementarydata.docx